Mechanisms of interference between motor memories

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OPENING

1

INTRODUCTION

Every day we execute a large number of movements: simple movements, such as picking up a cup of coffee and more demanding tasks, like riding a bicycle. We make all these movements seemingly automatically without paying much attention or thought. When walking, we do not think about where to place our foot next, or how to avoid obstacles, or how to coordinate the muscles that move our legs (Bernstein, 1967). Because of the automatic nature of movements, we may not realize how complex the underlying neural computations are. Complex computations are often linked to problems that require a lot of thought to solve, as for example the game of chess. These thoughts can be simulated artificially: IBM's chess-playing computer "Deep Blue", able to evaluate 100 million different chess positions per second, defeated grandmaster Garry Kasparov in a memorable match in 1997. In this game, Deep Blue indicated the new coordinates on the chess board of the particular piece that should be repositioned, but without actually physically moving the piece. As to the latter problem – making the movement – we still have not been able to build a robot that exceeds the performance of a 4-year-old child. What makes the generation of such a seemingly simple movement so dauntingly complex?

First, sensory information has to be gathered about the external world through the eyes (where is the chess piece relative to me) and about the current state of the arm (where is my arm and what is its configuration) sensed through proprioception and other internal senses. Next, this information has to be combined, a process called sensory integration. Based on this information, a neural command needs to be formed that precisely controls each of the ~23 arm muscles to produce the torques in elbow and shoulder that together yield a smooth reaching movement toward the chess piece. Each of these steps needs to be executed at every point in time, which requires extraordinary levels of computation and co-

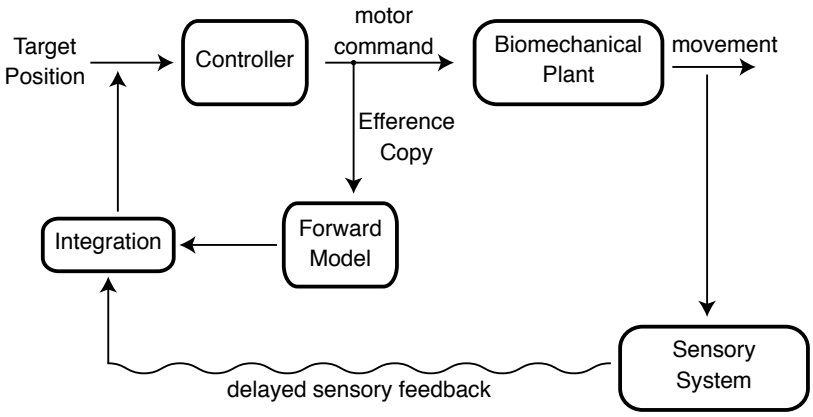


Figure 1.1: Model of motor control incorporating feedforward and feedback control. Based on a target position, a motor command is generated by the controller, which incorporates an inverse model. This motor command leads to movement of the respective body part, here referred to as biomechanical plant. This is called feedforward control. The produced movement is sensed by the sensory system and fed back to the controller. This is called feedback control. The sensory feedback however is delayed. To overcome this delay an internal estimate is created based on a copy (efference copy) of the used motor command. The efference copy is fed into the forward model, which maps motor commands to sensory consequences. The internal estimate and the delayed sensory feedback are combined before fed back to the controller.

ordination. Chess is just one example, not considered a sport requiring a lot of dexterity. Other sports like tennis or baseball are characterized by a much higher need of dexterity.

1.1 OPEN-LOOP VS FEEDBACK CONTROL

Every movement we make is based on two important parts: open-loop and feedback signals (figure 1.1). Open-loop predictions are made prior to the movement, based on previous experience. However, what if dur-

ing the movement something unexpected were to happen, for example a push to the arm while reaching for the chess piece? Open-loop control does not observe the output of the processes that it is controlling, and therefore cannot compensate for possible disturbances. Because we can never perfectly predict the future, there is feedback control, which corrects our movements during execution. In this case, the disturbance of the arm is sensed visually and via proprioception. With that information, the movement is corrected so that our arm still ends up at the chess piece, as intended.

A downside of feedback control is that sensory signals are delayed. Information about the current state of the arm is readily outdated: as soon as the information arrives at the brain, the arm has already adopted a new state (Franklin and Wolpert, 2011). To allow accurate and flexible movements at the same time, it is important to overcome this problem of sensory delay. To do so, the brain makes use of feedforward control mechanisms, which rely on internal estimates of body parts' configurations, which are available without noticeable delay. To compute these estimates, the brain uses copies of the current motor commands, called efference copies (figure 1.1). This efference copy is fed into a forward model, which is a neural process that simulates sensory outcomes of the motor system based on this signal. The forward model thus entails a mapping of motor commands to predictions about the sensory consequences. The opposite mapping, from desired sensory outcomes to motor commands is called the inverse model. Both forward and inverse models are collectively termed internal models (Wolpert et al., 1998).

The existence of internal models can be demonstrated using a simple example: place a heavy book flat onto your hand and then pick it up with your other hand. You will notice that your hand that carried the book remains at the same location in space. This is nothing exciting, but now place the book back onto your hand and let someone else pick it up. As soon as the other person picks it up, your hand that carries the book will move up. The difference between these two cases is that in the first, where you pick up the book yourself, you use feedforward control, whereas in the other case you can only rely on feedback control. In other words, in feedforward control you know the weight of the book and you

know that as soon as you pick it up what the sensory consequences will be based on your internal estimate. Due to this additional information your hand that carried the book remains at the same position in space. In feedback control you cannot predict the exact time and speed of the other person's lift of the book and you can only respond with a delay on observed actions and the resulting errors.

We typically make use of a combination of feedforward and feedback control when guiding movements. Many models have been proposed on how feedforward and feedback mechanisms interact. One contemporary framework is called optimal feedback control (OFC), which describes these interactions as the solution of an optimization problem.

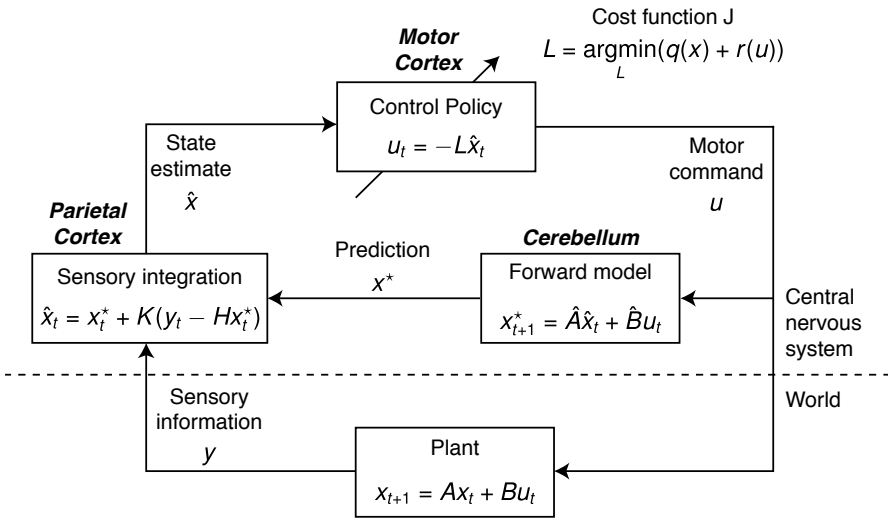
BOX 1: OPTIMAL FEEDBACK CONTROL

As simple as reaching movements appear to us, there is an infinite number of ways we can perform a reach to a target. However, given this abundance of possibilities, the reaching movements we perform are rather stereotyped having a slightly curved path and a bell-shaped velocity profile (Morasso, 1981; Atkeson and Hollerbach, 1985). What could be the underlying mechanism for this similarity?

It has been proposed that the stereotypical reaches we perform emerge by optimizing properties of the movement itself. Several cost functions have been proposed over the last 4 decades, such as optimizing kinematic smoothness, called the minimum jerk hypothesis (Flash and Hogan, 1985), smooth changes in joint torques, called the minimum torque change hypothesis (Uno et al., 1989) to minimization of endpoint variance, called the minimum variance hypothesis (Harris and Wolpert, 1998). However, all these models make predictions about the desired movement path.

In 2002 an alternative framework was proposed, called optimal feedback control (OFC, Todorov and Jordan (2002)). In OFC there is no ideal path, but a set of constraints that together form a cost func-

tion. Based on this cost function and the limb dynamics an optimal control policy is computed for the movement. This control policy is then used over the whole movement to create motor commands resulting in muscle contractions forming a movement. As before, a copy of the motor command (efference copy) is sent to the forward model to create an internal estimate, which is immediately available to the system. The slower sensory feedback loop is combined with the internal estimate by being weighed with respect to their individual reliability. After sensory integration, the state estimate is fed back into the controller (i.e. the control policy) and the loop is completed.



Box 1 figure: Details of the optimal feedback control model adapted from Diedrichsen et al. (2010). The motor command (u), results in a movement of the body. The current state of the environment and the body is captured by the state vector x, which is defined by the state-dependent matrices A and B. Due to the fact that sensory feedback $y_t = Hx_t$, is delayed in time, an internal estimate (x^*) is calculated by using an efference copy of the motor command u.

The efference copy is then fed into a forward model, which generates predictions of the next state. The state estimate ($\hat{x}$) is generated by combining the internal estimate (x^*) and the sensory feedback (y_t). Each is weighed relative to their reliability, the inverse of their variance. The next motor commands are then determined using a control policy. The control policy comprises a set of rules defining what to do with respect to a task goal and the state estimate. The goal of the control policy is to minimize a cost function, J. The cost function entails two components: $q(x)$, which defines external goals relative to incorporated states; $r(u)$, a regularization term that penalizes unnecessary motor commands (u), by taking their weighted sum of squares.

1.2 INTERNAL MODELS

Imagine you were to reach for a chess piece many times in a row, each time being disturbed by a push to your arm. What would happen? Because your arm is deviated from the ongoing trajectory, feedback signals kick in to guide it back on track. However, over the course of many reaches, your deviations become smaller and smaller despite the fact that your arm is still being disturbed by a push every time. Why would your performance improve?

This happens because the sensory prediction from your internal model and the actual sensory feedback are compared, resulting in a mismatch called sensory prediction error. This error is then used to adjust or create a new internal model. The new mapping of motor commands and sensory outcomes then leads to better predictions and reduced errors when your arm is being pushed. This example illustrates that internal models need to be learnt. They are part of our memory – a motor memory – and are constantly adjusted, newly created and reactivated when necessary.

To study internal models or motor memories, adaptation paradigms are used. Common laboratory paradigms involve adaptation of reaching movements to perturbations such as visuomotor rotations (figure 1.2A).

A visuomotor rotation creates a kinematic mismatch between desired and actual movement (Krakauer et al., 2005). Think about your mouse cursor: A 30° rotation of the mouse would mean that if you move your mouse forward, your cursor would not move up on your screen, but would deviate 30° to the right (figure 1.2A). To compensate for this and make your cursor move up again you need to move your mouse 30° to the left. This kind of perturbation results in learning a new kinematic mapping. Another perturbation paradigm would be a force field (figure 1.2B), which creates dynamic mismatches by imposing forces that deviate the hand from a desired path, similar to the push to the arm while reaching for the chess piece. How would that look like in the lab? To create force fields in the lab, robotic manipulanda are used (figure 1.2D). For example, the vBOT is a robotic manipulandum consisting of a two-link arm with a handle at its end (Howard et al., 2009). The links of the manipulandum are connected to motors, which can create any kind of force environment in a two dimensional plane. Imagine you are holding the handle of the manipulandum and are supposed to make a movement from close to the center of your body in the forward direction. In the normal case that reaching movement would be rather straight. However, if a velocity-dependent (viscous) force field is acting on the handle your hand will be pushed off the straight path because the force is proportional to the velocity and perpendicular to the direction of your reach. This can occur either to the right (clockwise, CW; figure 1.2B red), or to the left (counterclockwise, CCW; figure 1.2B blue), relative to your reach direction. Unlike visuomotor rotations, the feedback of your hand position is still accurate, but a new combination of motor commands needs to be learnt in order to make straight movements again.

Learning can be assessed by quantifying the reduction in reach errors from a straight line over time. The pattern of error reduction typically follows an exponential decay function:

$$error(n) = E_0 \cdot e^{-\frac{n}{\tau}} + E_f \tag{1.1}$$

Here, n refers to a trial, $E_0 + E_f$ represent the error at the beginning of learning, τ is the time constant of adaptation, and E_f is the offset repre-

senting the final learning plateau. The learning speed (τ) is assessed by fitting this exponential function to the data.

Another way to assess learning is to look at the compensatory strategy itself. One indicator for a compensatory strategy is called the aftereffect (Shadmehr and Mussa-Ivaldi, 1994). Aftereffects can be shown by interspersing perturbation trials with regular trials where no perturbation occurs (null trials). Because these trials cannot be anticipated, participants will compensate for the perturbation as learnt, but the perturbation is not applied. This leads to curved reaches that typically go in the opposite direction of the usual perturbation. The size of aftereffects depends on the amount of compensation that is present after learning. While at the beginning of learning compensation is small, it gradually becomes larger, plateauing when the learning has been completed.

The disadvantage of examining aftereffects in learning paradigms is that they provide error feedback that, in turn, affects the adaptation process. Because the error in this case goes in the opposite direction, it will therefore lead to "unlearning". To overcome this problem, but to still directly observe the compensatory strategy, so-called error-clamps have been developed. Error-clamp trials do not provide any type of error feedback and can therefore assess the amount of adaptation without inducing "unlearning" (Scheidt et al., 2000; Smith et al., 2006). For example, in force field learning experiments this is accomplished by enforcing a straight reach by creating a strong enough force "channel" between start and target position (figure 1.2C). The force against this channel produced by the subject during the reach is measured and compared to the hypothetical force perturbation. The hypothetical perturbing forces are the velocity dependent forces that the subject would have experienced if this had been a force field trial.

1.2.1 *Generalization*

An important aspect concerning internal models is that they generalize. Generalization refers to the act of responding to a stimulus similar but distinct from the trained stimulus. In other words, the internal model

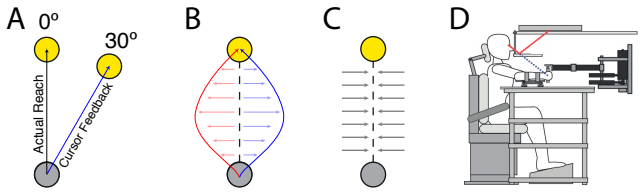


Figure 1.2: Exemplification of visuomotor and force field perturbation and an error clamp. **A.** A 30° visuomotor roration creates a mismatch between an actual movement and its feedback. Reaching towards 0° results in a 30° rotated cursor feedback. To make a cursor movement towards 0°, an actual reach towards -30° needs to be performed. **B.** Force field perturbation. Reaching towards 0° results in a deviation in a left (counter clockwise, CCW) or right (clockwise, CW) direction. The sensory feedback is still correct, however to create a straight movement again, new combination of motor commands need to be learnt. Shaded arrows exemplify the amount of perturbing force. **C.** Error-clamp. A straight reaching movement is imposed, by creating an artificial force channel. This way the amount of compensatory strategy can be assessed without inducing de-learning. **D.** Experimental setup. Subjects are seated in front of a robotic rig holding the handle of a planar robotic manipulandum. Adapted from Franklin and Wolpert (2008).

you acquired when learning how to ride a mountain bike can also be used for riding a road bike. The advantage is that we do not require learning one internal model for each particular movement we make. In the laboratory, generalization is typically measured by letting subjects adapt to a perturbation in one movement direction and then testing the amount of compensatory strategy at untrained movement directions (Donchin et al., 2003; Maschke et al., 2004; Izawa et al., 2012). It usually resembles a Gaussian-like shape, meaning that the compensatory strategy diminishes as the distance from the trained location increases (figure 1.5C). Note that 'distance' can be quantified in multiple reference frames (Berniker et al., 2014).

1.2.2 *Learning multiple internal models*

We constantly switch between internal models: reaching for a chess piece, riding our bicycle, or driving a car. This natural flexibility has also been tested extensively in the lab by using two opposing perturbations. For visuomotor rotations these could be a 30° versus a -30° rotation, whereas in force field learning this could entail a CW versus a CCW field (figure 1.2B).

To test if we can learn and maintain multiple internal models, experimentalists often use *ABA* paradigms. In this paradigm, subjects first learn to compensate for perturbation *A* over a large number of trials and subsequently learn to compensate for the opposite perturbation *B*. If the two internal models were learned independently, the second exposure to *A* should result in faster relearning. However, while we naturally switch between internal models in daily life, this flexibility is absent in the laboratory paradigms (Caithness et al., 2004). A general finding is that the second time we are exposed to *A*, our learning rate is the same and at times even worse than the first time. How could this be?

It has been suggested that interference prohibits a quick and smooth learning of the two models closely in time. Two types of interference are described, anterograde and retrograde interference (Krakauer et al., 2005). Anterograde interference describes how much current learning is affected by past learning. In the *ABA* paradigm anterograde interference exists for example for *B*, which can be affected negatively by having learnt *A* first. Retrograde interference on the other hand describes how much present learning affects past learning. In the aforementioned example this describes the opposite direction of influence, how much learning *B* affects *A*, which has been learnt before.

Anterograde interference can be reduced in an *ABA* paradigm by using a block of null trials (*AnBnA*). This way the compensatory strategy of *B* cannot be 'active' when *A* is suddenly reintroduced (Miall et al., 2004). However, even in this condition with only retrograde interference, we observe no faster relearning of *A*. But what has happened to memory *A*, while *B* was learnt?

Two mechanisms have been proposed that might be the underlying reason for the lack of faster relearning in the *ABA* paradigm. The first one proposes that memory *A* is erased while *B* is acquired (erasure hypothesis). The lack of faster relearning therefore results from the complete absence of memory *A* and it needs to be acquired again from scratch (Brashers-Krug et al., 1996). The second mechanism suggests that *A* is not erased by *B*, but that *A* is masked by *B* (Pekny et al., 2011). Thus, as soon as *A* is re-introduced the masking memory *B* is first expressed but gradually the mask is lifted and the memory of *A* is gradually re-expressed. In **chapter 4**, we study the erasure and masking hypothesis based on a novel paradigm that exploits the generalization curves of both memories.

1.2.3 *Contextual cues*

It has been suggested that the discrepancy between learning multiple internal models in the lab environment and our natural flexibility to switch internal models in daily life relates to availability of contextual cues in the natural world and the lack thereof in the laboratory. In daily life, actions take place in a rich context. For example, when riding a bicycle, the bicycle itself is already a contextual cue making sure we are not going to use the internal model of driving a car. In other words, we 'know' what to do and which internal model to update if we observe an error. Using more impoverished lab environments, researchers have tested various contextual cues to see whether they make learning and retention of multiple internal models possible in *ABA* paradigms. One study tested the role of static visual cues by changing the screen background associating one color with one perturbation (*A*) and another color with the opposite (*B*) (Gandolfo et al., 1996). Another study used haptic cues to inform participants which perturbation (*A* or *B*) they were going to experience (Cothros et al., 2008). In this case, subjects experienced a force field (*A* or *B*) that was linked to the shape of the handle of the robotic device. Other studies used explicit verbal instructions, informing subjects which perturbation (*A* or *B*) is coming up next (Miall et al., 2004). However, none

of these cues aided in faster relearning of *A* in the *ABA* paradigm. Do contextual cues not work in a lab environment?

The answer is that they can work, but that cues need to be of different nature. For example, if subjects moved with different wrist postures, each associated with a different perturbation (*A* or *B*), faster relearning was observed. Learning two internal models was also observed when each was associated with a different starting position of the hand (Hwang et al., 2006b). It is even possible to learn two opposite internal models simultaneously, i.e. when the two perturbations switch randomly if provided with an appropriate cue (Hirashima and Nozaki, 2012; Howard et al., 2012). For example, Howard et al. (2012) showed that two force fields are learnt at the same time when making use of pre-movement cues. These pre-movements are reaches from two different start locations to the same via-point where the second reach starts, which is perturbed by a CW or CCW force field (figure 1.3). The direction of the force field depends on the direction of the pre-movement, but the direction of the second, perturbed, movement is always the same.

In **chapter 2** and **3** of this thesis we study the role of contextual cues in more detail. In **chapter 2** we exploit the natural sensorimotor link between the vestibular system and motor system to test whether vestibular cues aid in learning and recalling multiple internal models in an *ABA* paradigm. In **chapter 3**, we test the properties of contextual cues in motor learning. We use pre-movements as contextual cues and test how they generalize, interfere, and transfer within and across effectors.

1.3 COMPUTATIONAL MODELS OF MOTOR LEARNING

Many computational models have been proposed to capture the way we form motor memories and their properties like interference. Two influential approaches are state-space models (figure 1.4) (Smith et al., 2006; Lee and Schweighofer, 2009; Pekny et al., 2011; Howard et al., 2015) and motor primitives models (Pouget and Snyder, 2000; Thoroughman and Shadmehr, 2000; Donchin et al., 2003; Poggio and Bizzi, 2004; Yokoi et al., 2014):

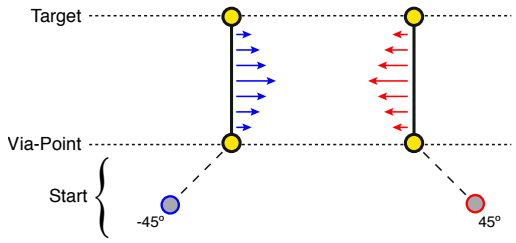


Figure 1.3: Pre-movements as contextual cues. First phase of moving is the contextual pre-movement part. A reach from a start position to the via-point is performed. The second phase is the perturbed reach, from via-point to target. Only in this part a perturbation occurs, whereas the pre-movement is unperturbed. The start position of the pre-movement (-45° or 45°) is indicative of the perturbation, which is going to occur in the 2nd phase of movement. Using pre-movements as contextual cues, two opposing perturbations can be learnt simultaneously.

1.3.1 *State-space models*

These types of models make use of the observation that a memory is governed by learning and forgetting processes. They incorporate these processes by using a forgetting factor and a learning rate (figure 1.4A, α and β). The forgetting factor determines how much of the memory from the previous trial will be maintained in the current trial and the learning rate determines how much the memory will be adapted based on the observed error. Modeling the process of learning this way captures the earlier discussed observations of adaptation, including interference (no faster relearning). It also captures the puzzling observations of spontaneous recovery (Smith et al., 2006).

Spontaneous recovery (figure 1.4B) refers to the observation that one internal model is re-expressed (recovers spontaneously) even though reaches are equivalent to baseline. A spontaneous recovery paradigm is structured as follows: first subjects are exposed to perturbation A, then shortly to perturbation B. Errors at the end of exposure to B already become small (figure 1.4B, blue). Next follows a series of error-clamp

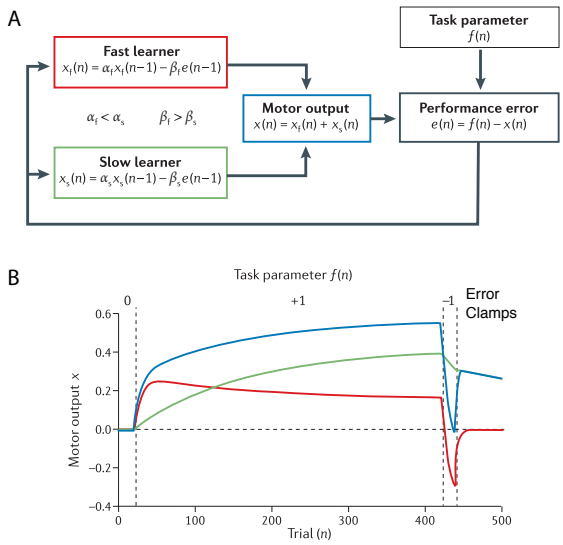


Figure 1.4: Multi-rate state-space model adapted from Wolpert et al. (2011). Red, fast process; Green, slow process; Blue, motor output. **A.** Both processes entail a forgetting factor (α) and a learning factor (β). The fast process forgets faster than the slow process ($\alpha_f < \alpha_s$) and also learns faster ($\beta_f > \beta_s$). The error (e) is calculated based on the difference between the perturbation $f(n)$ and the motor output $x(n)$, at each trial n. **B.** The output of each process in a spontaneous recovery paradigm. Standard adaptation occurs due to a mix of fast and slow process contribution. Initial contribution of the fast process is large and diminishes over time. The slow process contributes more over the course of learning. When an opposite perturbation is introduced the fast process is responsible for a fast decrease in error. During the following error-clamp period the observed spontaneous recovery occurs due to the slow process.

trials (figure 1.2C). What happens during the block of error-clamp trials is that the compensatory strategy of *B* is used at first but then gradually switches back to *A* (figure 1.4B, blue). *A* therefore spontaneously recovers.

This observation cannot be captured by a single-rate state-space model, but points toward multiple timescales of memory (Smith et al., 2006). It has therefore been suggested that two learning processes run in parallel, a fast and a slow process. The fast process learns fast, but also forgets fast (figure 1.4, red), whereas the slow process learns slowly, but forgets slowly (figure 1.4, green). The estimated perturbation magnitude is based on the summed estimate of both processes and this determines the motor output (figure 1.4, blue). In a spontaneous recovery paradigm, the quick adaptation to *B* is driven by the fast process (figure 1.4B, red), whereas the re-expression of *A* is caused by the slow process that is lagging and has not transitioned to *B* yet (figure 1.4B, green).

In this form, state-space models are able to explain spontaneous recovery and interference, but lack the ability to acquire multiple motor memories simultaneously (Lee and Schweighofer, 2009). To be also able to acquire multiple motor memories, state-space models have been extended with a contextual cue factor, which allows switching from one internal model to another. Research has suggested that this factor should be implemented in the slow process only. If incorporated in the slow process, the state-space framework could also also capture results from many multiple internal model learning studies (Lee and Schweighofer, 2009). However, this framework does not provide a mechanism that drives the contextual cue switch. The switch itself is arbitrarily driven by the predetermined contextual information.

1.3.2 *Motor primitives*

It is important to point out that state-space models can only explain the development of error over the course of learning. They do not capture generalization. However, generalization is an important property of the

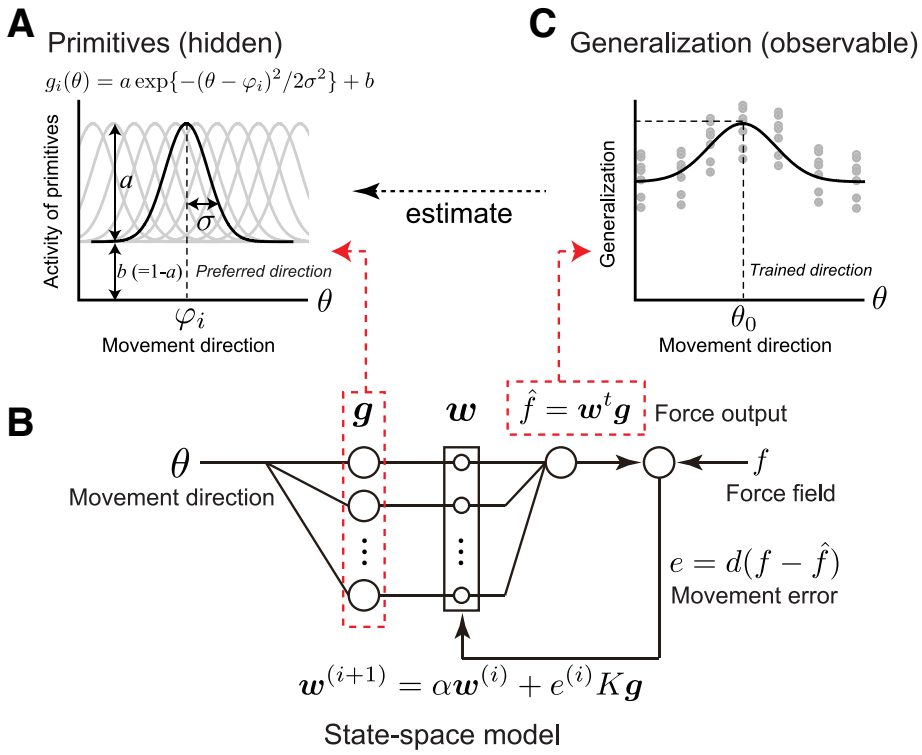


Figure 1.5: Motor primitives model adapted from Yokoi et al. (2014). Network of primitives g code across space, movement direction (θ). A. Each primitive g is defined by a Gaussian-like tuning function, comprised of a preferred direction (φ), a width parameter (σ), gain (a) and an offset (b). **B.** Every primitive g is linked to a weight w. The linear combination of g and w results in the motor output ($\hat{f}$). As in the state-space model (figure 1.4), the error is computed and the weights are updated using a forgetting factor (α) and a learning factor (K). **C.** The network of primitives can capture the observable generalization behavior in adaptation paradigms.

internal model and may provide important insights into how the internal model is encoded neuronally (figure 1.5).

To model adaptation and generalization simultaneously, often a network of basis functions is used (Pouget and Snyder, 2000; Thoroughman and Shadmehr, 2000; Donchin et al., 2003; Poggio and Bizzi, 2004; Yokoi et al., 2014). A basis function is supposed to emulate the firing properties of an individual neuron. Its tuning function determines its response to a given stimulus. Usually Gaussian-like tuning functions are used. The network then codes for responses across the entire movement space, where every neuron codes for a specific part of the state space, centered at its preferred direction (*PD*) (figure 1.5A). Each neuron is also associated with a contribution factor, its so-called weight. Learning is incorporated by changing the weights of the neurons, based on their *PD* and the observed motor error. In other words, if reaches were just trained in a 90° direction, only neurons that have their *PD* close to 90° will have their weights adjusted. The way the weights are adjusted is exactly like in the aforementioned state-space models using a forgetting and a learning factor. After adaptation, this network can then be tested in all directions and shows the similar generalization patterns as behaviorally observed.

Just like an exponential function or a state-space model can be fit to learning data to assess learning speed, the motor primitives model can be fit to the behaviorally observed generalization pattern (figure 1.5C) to draw inferences about changes in encoding (figure 1.5A). For example, Yokoi et al. (2014) used a bimanual adaptation task, in which either the left of right hand was exposed to a force field. After learning the force field in one direction (figure 1.5C, θ_0), generalization was assessed by performing movements in all possible directions using error-clamps (figure 1.5C, grey data points). Next they used a motor primitives model, which was equivalently trained to a force field in one direction (θ_0). At the heart of a motor primitives model are the primitives g, which are tuning functions with a preferred direction and tuning width (σ). After training, this motor primitives model was simulated for different movement directions as input (θ), which revealed a generalization pattern. The preferred directions and tuning widths of the primitives were directly linked to this pattern. (figure 1.5C).

Thus, to make inferences about changes in encoding, the generalization of the motor primitives model can be fit to the behaviourally observed generalization, with the tuning width (σ) as a free parameter. Doing this for the two different hands that have been trained, revealed a sharper tuning in the encoding for the left than for the right hand.

Another advantage of this neural network approach is that not only the underlying changes in encoding are determined, but that also the learning mechanism itself is simulated. Thus far, it has been assumed that during learning, the updating process (changes of weights) takes place relative to the target direction, i.e., where we plan to move (Pouget and Snyder, 2000; Thoroughman and Shadmehr, 2000; Donchin et al., 2003; Poggio and Bizzi, 2004; Yokoi et al., 2014). Reaches in the 90° direction would lead to weight adjustments of neurons coding that particular part of the state-space. However, recent research has shown that this may not be the case. Rather than learning relative to where we want to move, i.e. in the 90° direction (plan-referenced learning), we seem to learn relative to where we are moving (motion-referenced learning) (figure 1.6A). This means that if we were to reach in the 90° direction but a perturbation causes us to perform the reach in the 70° direction, weights around the 70° reach direction will be updated (Gonzalez Castro et al., 2011). Over the course of learning, reaches will still converge toward the 90° direction. This results in very different predictions of generalization, especially at the beginning of learning. Motion-referenced learning predicts a shifted and skewed generalization curve in the direction of error. In contrast, plan-referenced learning predicts a generalization curve centered around the trained target direction (figure 1.6A and B). In **chapter 5**, we investigate how different levels of interference, induced by learning two force fields simultaneously, change neuronal encoding and the learning mechanism (plan-referenced or motion-referenced learning).

1.4 BRAIN STRUCTURES

Extensive research has been done to determine which brain regions are involved in the acquisition of internal models. One crucial brain region

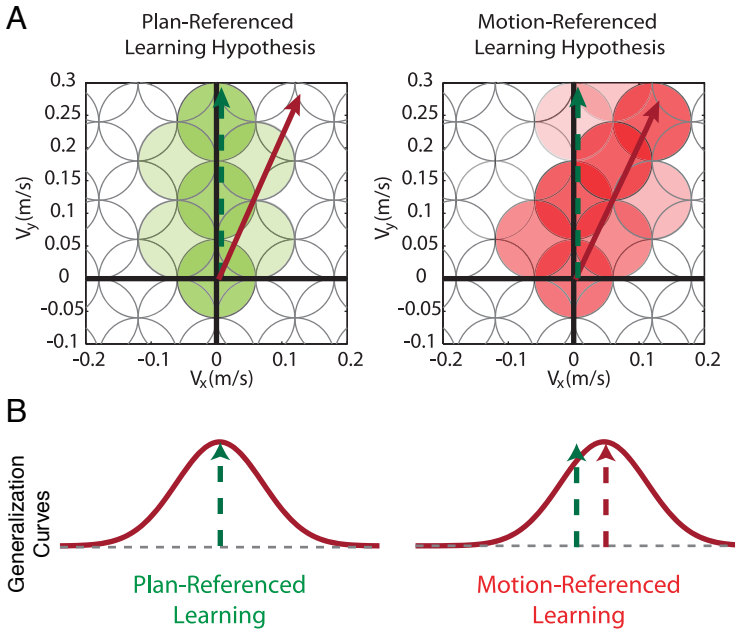


Figure 1.6: Illustration of plan-reference learning versus motion-referenced learning, adapted from Gonzalez Castro et al. (2011). **A.** Green arrow denotes a planned reach; red arrow denotes the actual performed reach due to a perturbation. In plan-referenced learning, primitives relative to the green arrow would be updated. Whereas in motion-referenced-learning, primitives relative to the red arrow would be updated. **B.** The difference in updating mechanism would cause a shift of the generalization curve in the direction of error.

is the cerebellum. In a well-known study, healthy controls and cerebellar patients are instructed to throw balls while wearing prism goggles. Prism goggles cause a shift of the visual feedback, and similar to visuomotor rotations, require learning of a new kinematic mapping. Healthy control subjects learned this new mapping appropriately as shown by smaller throwing errors with the number of performed trials. However, cerebellar patients did not show any improvement, regardless how many trials were tested (Martin et al., 1996a,b). This shows that the cerebellum is a crucial area involved in learning internal models.

Further evidence for the involvement of the cerebellum comes from single cell recordings. The recordings revealed that Purkinje cells encode movement parameters like position, velocity, and direction (Ebner et al., 2011). This information is indicative of internal model coding as it is present before actual feedback could be assessed. Also brain stimulation studies, disrupting cerebellar function using TMS (transcranial magnetic stimulation), highly impaired our ability to make accurate internal estimates (Miall et al., 2007). In the experiment of Miall and colleagues, participants had to make a slow lateral movement. At a random moment in time, a cue was given that instructed a quick reaching movement to a static target in front of them. To make an accurate reaching movement to the target, up-to-date information about the hand's position at the time of the cue is vital. In case the information is out-dated, inaccurate reaching occurs, because the hand will initiate a reach 'thinking' it is at a specific position, but which it already left. Participant's behavior showed that if TMS was delivered over the cerebellum at the time of the go cue, end-point errors of the reach increased significantly. This suggests that the cerebellum is involved in calculating the internal estimate.

Learning can be enhanced by tDCS (transcranial direct-current stimulation) - a relatively new method in cognitive neuroscience. tDCS is a brain stimulation technique, which passes a current through the brain. If the cerebellum is stimulated using tDCS during learning, learning rates increase significantly. Interestingly, stimulation of M1 during learning did not increase the learning rate, but reduced the forgetting rate (Galea et al., 2011). This effect could be explained by the two-rate state-space model: stimulation of the slow process would not result in huge differ-

ences in learning rate, but could boost retention. On the other hand, a boost of the fast process would result in a higher learning rate. This would suggest that the slow process resides in M1 and the fast process in the cerebellum. However, proof of this analogy does not exist (yet).

These findings for M1 are corroborated by reports of changes in M1 neurons' tuning curves in response to motor adaptation. The general finding is that the preferred direction (PD) of single neurons in M1 shifts towards the direction of the imposed force field (Li et al., 2001; Arce et al., 2010; Cherian et al., 2013). Some studies (see Cherian et al., 2013) have reported that these changes of PD in some neurons are sustained, even after adaptation has ended. It has been suggested that these cells – called memory cells – could form the basis for the behaviorally observed savings.

1.5 OUTLINE OF THIS THESIS

The main focus of this thesis is to investigate mechanisms of interference between motor memories. In **chapter 2**, we investigate the ability to learn multiple internal models when using the vestibular signal as a potential contextual cue. Human subjects performed reaching movements, while sitting on a vestibular sled. During reaching the sled was accelerated perpendicular to the reach direction. The acceleration of the sled caused deviations of reaches due to the arms inertia. At the same time the acceleration was sensed by the vestibular system, which might serve as a cue to disambiguate the two acceleration environments and update the correct internal model. The experimental paradigms were structured to test faster relearning under full interference conditions (*ABAB*), where both anterograde and retrograde interference are active, and under reduced interference conditions (*AnBnAnB*), entailing mainly retrograde interference. We show that subjects can adapt to this accelerating environment and that faster relearning occurs, regardless of interference levels. Furthermore, we suggest that the difference between effective and ineffective contextual cues lies in their involvement in the sensorimotor loop (figure 1.1, OFC Box).

In **chapter 3**, we examine the properties of contextual cues using pre-movements (figure 1.3). Subjects adapted to two force fields simultaneously based on two pre-movement cues. After adaptation, generalization of the pre-movement cues was tested at untrained pre-movement directions in the trained and untrained hand. Our results show that pre-movement cues generalize in a Gaussian-like fashion and that this pattern transfers to the untrained hand.

Chapter 4 investigates why no faster relearning of *A* is observed in *ABA* paradigms without contextual cues. It has been suggested that no faster relearning occurs due to one memory erasing the other (erasure hypothesis). However, no faster relearning could also occur due to one memory masking the other, meaning they both coexist but the wrong memory is expressed during re-exposure (masking hypothesis). To distinguish between these two hypotheses, we use the generalization properties of internal models as their unique signatures. We show that traces of the first internal model's (*A*) occur in the generalization curve of the second learnt internal model (*B*). This result supports a masking mechanism.

In **chapter 5**, we draw inferences about changes in neuronal encoding of motor memories induced by different levels of interference. Subjects had to adapt to two opposing force fields simultaneously. The force fields were linked to different target directions. The angular separation between the two targets was systematically varied to introduce different levels of interference. Our results show that higher levels of interference deterred learning, both in rate of learning and in final level of learning. Fitting a motor primitives model to the generalization and learning data suggests that neuronal tuning curves become narrower and the learning mechanism shifts from motion to plan-referenced learning with increasing levels of interference.

In the final **chapter 6**, we provide a summary of this thesis and an overview of additional implications and suggestions for further research.

1

Part II

EXPERIMENTAL CHAPTERS

2

VESTIBULAR BENEFITS TO TASK SAVINGS IN MOTOR ADAPTATION

Adapted from:
Sarwary AME; Selen LPJ; Medendorp WP (2013). *Vestibular benefits to task savings in motor adaptation*, Journal of Neurophysiology, 110: 1269-1277

2.1 INTRODUCTION

Motor adaptation is the process of regaining or retaining a given level of motor performance (Shadmehr and Wise, 2005). It has been shown that subjects readily adapt reaching movements to visual or force perturbations, suggesting that the brain forms and updates an internal model of the body and its interactions with the world (Shadmehr and Mussa-Ivaldi, 1994; Brashers-Krug et al., 1996; Caithness et al., 2004; Nozaki et al., 2006; Howard et al., 2010; Izawa et al., 2008). However, it is unclear how many internal models can be formed without interfering.

Daily life experience suggests no limit. In tennis we do not forget the forehand swing when learning the backhand stroke. Thus, we seem capable of simultaneously representing different dynamics associated with different contexts, suggesting multiple internal models can be formed, adapted and consolidated independently (Kawato, 1999). This, however, is at odds with laboratory findings.

Experiments with haptic interfaces have shown that the memory of one task is lost (Brashers-Krug et al., 1996; Caithness et al., 2004), or cannot be recalled (Pekny et al., 2011; Criscimagna-Hemminger and Shadmehr, 2008) after learning an opposing task. Associating each task with a different context by adding static visual (Gandolfo et al., 1996) or haptic cues (Cothros et al., 2008), does not improve recall of the memory. However, if tasks are distinguished by dynamic sensorimotor contextual cues, there is evidence for learning and storage of multiple internal models (Nozaki et al., 2006; Howard et al., 2010; Malone et al., 2011; Hirashima and Nozaki, 2012; Howard et al., 2008, 2012). For example, when unimanual and bimanual tasks are linked to opposing force fields, interference is reduced in the arm that is involved in both tasks (Nozaki et al., 2006). Likewise, different limb configurations, such as wrist postures (Gandolfo et al., 1996) or starting hand positions (Hwang et al., 2006b) can aid in learning. Recently, also different targets in the visual domain (Hirashima and Nozaki, 2012) or different cueing pre-movements (Howard et al., 2012) were discovered to provide sufficient sensorimotor context to permit parallel learning of opposing force fields.

The key difference between static visual or haptic cues and dynamic sensorimotor cues is that the former do not affect the motor plan. This lack of task involvement may explain why such cues do not improve retention. In other words, they are not directly implicated in the circuits mediating online sensorimotor control and as a result do not provide sensorimotor context.

So far, however, the sensorimotor cues that have been studied were all presented prior to movement execution. Here we ask the question whether sensorimotor cues that are only available during the execution of a task can also aid in learning and retaining two internal models.

In the present study, we exploit the natural sensorimotor link between the vestibular system and motor system. Because of its specialized organs (semicircular canals, otoliths) for detecting rotational and linear accelerations, the vestibular system may well serve in detecting different inertial force environments and aid in attributing them to distinct internal models. To date, however, experiments on adaptation of reaching movements have typically been performed in body-stationary subjects (Brashers-Krug et al., 1996; Caithness et al., 2004) or under constant velocity whole-body rotation where the vestibular system no longer indicates movement (Lackner and Dizio, 1994; Dizio and Lackner, 1995).

We tested subjects making forward and backward reaches while their whole-body was linearly accelerated either leftward or rightward on a vestibular platform (see Fig. 2.1a). The coupling between reaching and whole-body acceleration made vestibular information only available during arm movement execution. Reaches were made between the same initial and final hand positions, irrespective of the vestibularly-detected direction of body motion. We show that the vestibular system (i.e. otoliths) not only facilitates the estimation of the imposed forces, but also provides a contextual signal aiding in learning and recalling multiple internal models.

2.2 MATERIALS AND METHODS

2.2.1 *Participants*

Experiments were conducted under the general approval for behavioral experiments by the institutional ethics committee. 38 right-handed naïve subjects gave their written consent to participate in the experiments. Reimbursement was provided in terms of course credit or payment. All subjects had normal, or corrected to normal, vision and had no known motor deficits. Five subjects were excluded from the analyses based on their failure to develop internal models of the tested task environments (see section "catch trials" for further details).

2.2.2 *Setup*

Subjects performed reaching movements with their right arm, while sitting on a linear sled that moved along a magnetic track. The sled, powered by a linear motor (TB15N, Technotion, Almelo, The Netherlands), was controlled by a Kollmorgen S700 (Danaher, Washington DC, USA) drive. The sled chair was configured such that participants were seated with the interaural axis aligned with the sled's motion axis. Participants were restrained using a 5-point seat belt and their head was firmly fixated using an ear-fixed mold. Integrated earphones provided auditory instructions and feedback during the experiments. Emergency buttons at either side of the sled chair enabled subjects to stop the sled motion immediately if needed.

The tip of the right index finger and the sled position were recorded at 250 Hz using an Optotrak Certus system (NDI, Northern Digital Instruments, Waterloo, Canada) and stored for off-line analysis. Reach start and target positions were body-fixed and indicated by green and red LEDs, integrated into a table. This stimulus table was mounted on the sled, in front of the subject, and further served as an armrest in between trials (figure 2.1).

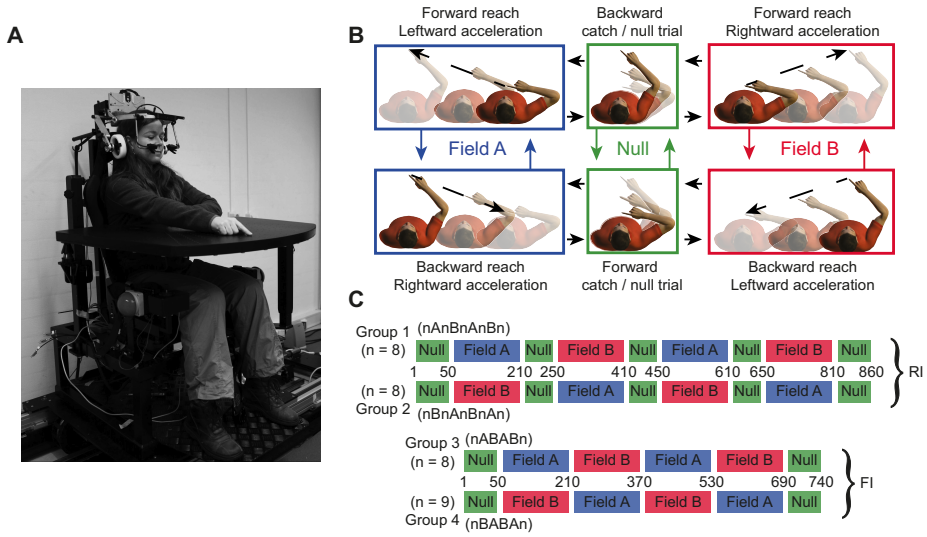


Figure 2.1: Experimental setup and paradigms. *A*: subjects were seated on a linear sled and performed right-hand reaching movements to visual targets presented on a sled-mounted table. *B*: force pairings. Pairing A (blue) consists of forward reaches linked to leftward accelerations and backward reaches linked to rightward accelerations. Pairing B (red) consists of forward reaches linked to rightward accelerations and backward reaches linked to leftward accelerations. During null and catch trials (green) the sled remained stationary. Arrows indicate possible trial transitions. *C*: experimental paradigms. In the reduced interference (RI) paradigm, force pairings are interspersed with 40 null trials. In the full interference (FI) paradigm, force fields follow directly after each other.

During the experiment, the sled accelerated laterally with a bell-shaped velocity profile of 650 ms duration and 30 cm amplitude with a maximum acceleration of 4.1 m/s2. Sled movement was triggered by the initiation of the reaching movement, derived from real-time Optotrak data recorded at 100 Hz (max. loop delay 40 ms). This results in a time-dependent force environment. Time-dependent force fields have been shown to be (mis)interpreted as state-dependent fields, which makes them more difficult to learn (Conditt and Mussa-Ivaldi, 1999; Karniel and Mussa-Ivaldi, 2003). The setup and experiment was controlled using custom software written in Delphi.

2.2.3 *Task*

Subjects had to perform 35 cm alternating forward and backward reaching movements. Inertial forces were introduced by lateral sled accelerations. Start and target positions were indicated using a green (start) and red (target) LED, which were aligned with the subject's mid-sagittal plane. During the sled movement, the start and target LEDs moved with the subject, i.e. they were body-fixed.

Participants initiated a trial by positioning their right index finger onto the green start location. A go beep was given after the finger had been within a circle with a radius of 1.5 cm centered at the start location and its speed had stayed below 2.5 cm/s for 500 ms. The start of the reach was determined as the first time point after the go beep at which the finger speed exceeded 2.5 cm/s. The endpoint of the reach was defined as the first point where finger speed was below 2.5 cm/s. If this point was outside the target area (radius of 1.5 cm), participants received auditory feedback that they missed the target ('please, aim better'). If this point was inside the target area, participants received auditory feedback about whether their reach time was below ('move faster'), within ('well done'), or above ('move slower') the required time window of 600 - 800 ms.

During the perturbation trials, the lateral sled accelerations resulted in inertial forces on the subject's arm and body. Subjects were instructed to perform reaches as naturally as possible, not to slide their finger or arm

over the table surface and to stay within the allowed time window. Experiments were performed under dimmed light to improve saliency of the body-fixed targets. Subjects could not make use of any visual anchoring points to assess amplitude or direction of the chair displacement.

2.2.4 *Experimental paradigms*

Our main interest is the degree of interference and retention of motor memories when learning two dynamical environments. Two opposing force environments were created by changing the couplings of the reach direction (forward and backward) and acceleration direction of the sled (leftward and rightward). By testing two reach directions, instead of just forward reaches, the overall learning rate is decreased, which allows scrutinizing the characteristics of adaptation in more detail. Furthermore, using two reach directions also improved the flow of the experimental paradigm as the sled moved back and forth on its rail from trial to trial staying within its limited movement range.

Pairing *A* consisted of a forward reach combined with a leftward acceleration and a backward reach combined with a rightward acceleration. For pairing *B* these couplings of reach direction and acceleration direction were reversed (figure 2.1b). To assure that observed effects are not due to the order of presented force environments, each paradigm included two subject groups tested with the opposite order of force pairings. We further manipulated the amount of potential interference by using two paradigms: a reduced interference (RI) and a full interference paradigm (FI) (figure 2.1c).

Reduced Interference Paradigm (RI). Subjects performed a familiarization block (50 reaches) without sled accelerations (null trials). This block was followed by 4 perturbation blocks (160 reaches each) with alternating force pairings: one pairing for perturbation blocks 1 and 3 and the opposite pairing for blocks 2 and 4. Retrograde interference occurs when learning of a force environment interferes with the memory of a previously learned environment; interference is anterograde when learning of the first environment interferes with the learning of the second.

The latter was minimized here by interspersing the perturbation blocks with blocks of 40 wash-out trials (null trials). Each perturbation block included 14 catch trials, in which the sled unexpectedly remained stationary (similar to the null trials, figure 2.1b). Catch trials were implemented on 7 forward and 7 backward reaches. They were randomly introduced with a minimum separation of 5 trials. Furthermore, catch trials evoke forward and backward reaching movements randomly at either side of the sled, even though sled motion alternates. This reduces the likelihood of subjects being able to use an explicit strategy based on sled position to dissociate between the two force pairings. The initial 20 trials of a perturbation block were catch trial free and every subsequent bin of 10 trials contained one catch trial. After the final perturbation block a de-learning block followed (50 reaches), which was equivalent to the familiarization block (null).

Full Interference Paradigm (FI). As we will show in the results, in the RI paradigm subjects were able to retain the learned dynamics after having learned the opposite force pairing in between. Therefore we set out to explore whether this observation also holds when both retrograde and anterograde interference are involved. The structure of this FI paradigm was equivalent to the RI paradigm except that the four perturbation blocks directly followed after each other without being interspersed by intervening blocks of wash-out trials (figure 2.1c).

2.2.5 *Analyses*

Data were analyzed off-line using Matlab (The Mathworks). Fingertip positions were first preprocessed. Missing data points, which were the result of an occlusion of an Optotrak marker during the reach, were reconstructed using spline interpolation. Position data were subsequently filtered using a 5th order, 12 Hz low-pass bi-directional Butterworth filter. All trials were used for analysis.

As we show in the results, the deviation of the reaching movement from a straight line joining start and target position changes over the

course of a block of trials. To quantify this deviation, we computed the signed hand-path error (E) defined as:

$$E = \int_{t_0}^{t_f} x(t) \cdot \dot{y}(t) dt \tag{2.1}$$

where x(t) is defined as the time-varying perpendicular distance between the actual trajectory and a straight line from the start to target position, weighted by the signed velocity $\dot{y}(t)$ velocity of the movement in the direction from start to target (Franklin et al., 2003). Note that by using this measure we do not suggest that subjects intended to make straight-line reaching movements in our paradigms. We used signed x(t) and signed $\dot{y}(t)$ in the calculation of E such that forward and backward errors have the same sign in each of the force fields. Because errors differ in magnitude between forward and backward reaches, likely caused by differences in limb inertia, we collapsed forward and backward errors into pairs.

As a first step in testing our retention hypothesis, we computed the relative difference in E between the first and second exposure to the second force pairing (perturbation blocks 2 and 4) at three different stages of adaptation (initial, early, final). We tested whether the obtained values deviated from zero using one-sample t-tests.

Further, to quantify learning over time in each subject, hand-path error in each block of trials was fitted with a single rate exponential function:

$$E(n) = E_0 \cdot e^{-\frac{n}{\tau}} + E_f \tag{2.2}$$

in which $E_0 + E_f$ represents the error at the beginning of learning, τ the time constant of adaptation, E_f the offset representing the learning plateau, and n refers to a pair of trials. If a pair of trials contained a catch trial, the whole pair was excluded from the fit. All other pairs were included in the analyses. Fit parameters served to test the retention hypothesis that subjects learn a force environment faster during the second exposure. More specifically, this means that τ should be smaller for the second exposure but that neither $E_0 + E_f$ nor E_f should dif-

fer between the first and second exposure. To test this statistically, we log-transformed the values of the fit parameters to assure normal distributions, and compared values of first and second exposure to a force environment using paired t-tests.

Catch trials. Over the course of learning, subjects dynamically compensate for perturbing forces, resulting in a decrease in hand-path error. If these perturbations are unexpectedly removed (catch trials), compensation leads to an error in the opposite direction. Due to this reverse relationship, the hand-path errors in the catch trials reveal whether subjects establish an internal model during adaptation, by showing an increase over the course of learning. If hand-path errors during perturbation trials decrease with trial number, but are not paralleled with an increase of the error in the catch trials, subjects probably use an alternative strategy, for example an impedance control strategy (Franklin et al., 2003).

We used linear regression to test whether the error in catch trials increased with trial number in a perturbation block and only included subjects that did show a significant positive slope in exposure blocks 2 to 4. Based on this criterion, which is not related to any of our outcome measures, five out of 38 subjects were excluded from further analysis. Three of them were from group 1; the other two came from group 2 and 3.

2.3 RESULTS

We evaluated the adaptation and retention of human reaching movements in response to inertial force perturbations induced by whole-body lateral accelerations. Subjects were tested in two opposing force pairings, *A* and *B*, in which the direction of the reaching movement (forward-backward) was uniquely associated with the acceleration direction of the body (leftward-rightward) (figure 2.1b). We used these pairings in two different interference paradigms (figure 2.1c): reduced (RI) and full interference (FI). Within each paradigm, two subject groups were tested to balance for the order of the force pairings. We hypothesize that the vestibular system provides a strong contextual cue, which is indepen-

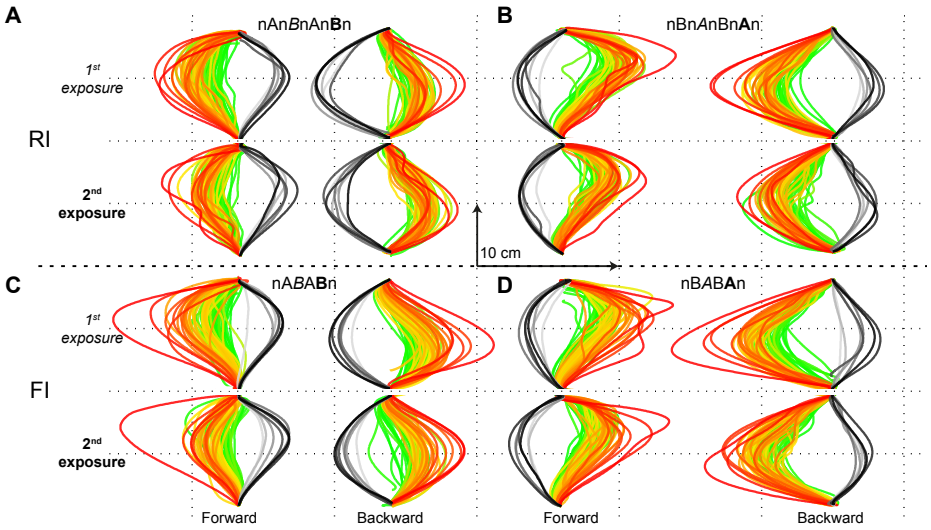


Figure 2.2: All forward and backward reach trajectories during the 1st and 2nd exposure block, averaged across subjects. Exponential color transition from red (initial trials) via yellow to green (final trials) is indicated. *A* and *B*: RI paradigm. *C* and *D*: FI paradigm.

dent of the reach error. This cue reduces task interference and therefore enables learning of the two opposing force environments. We start the description of the results by depicting the development of the reach trajectories over the course of learning. We will focus our analyses on perturbation blocks 2 and 4 because they have the same immediate history of force environments and therefore offer the fairest comparison.

2.3.1 *Reach trajectories during adaptation*

Figure 2.2 shows group average trajectories (forward and backward) for all trials, for all four subject groups (two paradigms x 2 force pairings) separately, color-coded by trial number. In all conditions, initial trajectories (red) in the first and second exposure blocks match closely, suggesting that adaptation started at the same level. The same holds for the final trajectories (green), suggesting that subjects reach the same level of

adaptation in the first and second exposure block. However, the red-to-green color gradient (orange-yellow), characterizing the time course of adaptation, is clearly different for the first and second exposure: In the second exposure block the trajectories converged faster towards the final adapted trajectory compared to the first exposure block.

To validate the adaptation effects, we computed the signed hand-path error (E, see Eq. 2.1) to quantify trial-by-trial changes of the reach trajectories. We examined the relative difference between E at three phases of the first and second exposure blocks: the initial trials (trials 1-2), the early trials (trials 9-13), and the final trials (trials 140-160). Figure 2.3 shows the mean (±SE) of the relative difference across all paradigms. One-sampled t-tests did not reveal a significant difference from zero for the initial ($p = 0.41$) and final ($p = 0.24$) reaches. By contrast, for the early reaches (orange bar), the relative difference was significantly larger than zero ($p < 0.001$), meaning E was significantly smaller for the second than the first exposure. This systematic difference suggests that, during the second exposure to the same force environment, subjects more quickly regained the performance level at which they ended the first exposure.

A noteworthy observation in figure 2.2 is that the final adapted trajectory (green) does not match a straight trajectory that is usually observed in initial control trials during which no perturbations are imposed (Izawa et al., 2008). The final trajectories are curved with a consistent maximum deviation of about 1-2 cm from a straight line. This suggests that subjects do not fully compensate for the imposed forces early in the reach and exploit the inertial forces, caused by the deceleration, to bring their hand on target (Izawa et al., 2008).

2.3.2 *Learning curves*

Above we only assessed retention at specific time points in the learning process (figures 2.2 and 2.3). To capture the temporal characteristics of reach adaptation we examined the signed hand-path error (E, see Eq. 2.1) in each block, as a function of trial pair. The blue and red dots in Figure 2.4 show these data, as an average across subjects, for the two force pair-

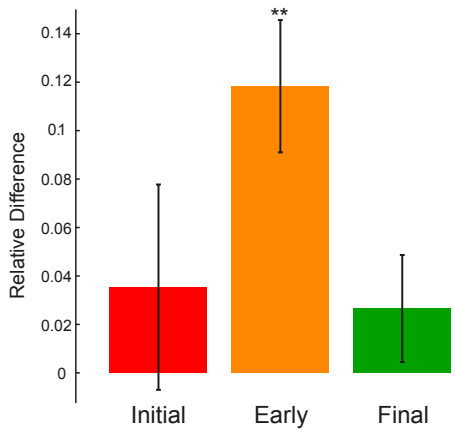


Figure 2.3: Relative difference (1st vs. 2nd exposure) of initial, early, and final hand-path errors (E; Eq. 2.1) across all subject groups. Bars denote SE. The relative difference only differs from zero for the early reaches.

ings of each paradigm. The black dots represent E of catch trials, which will be discussed below. Consistent with the observations in figures 2.2 and 2.3, hand-path error gradually decreases over the course of a perturbation block. We fit single-decaying exponential functions (Eq. 2.2) to each subject's data to estimate the learning curves. R^2-values ranged from 0.45 to 0.71 for all paradigms ($p < 0.001$). The parameters of the individual fits of perturbation blocks 2 and 4 are presented in Table 2.1. The time constant τ of the exponential fits quantifies the rate of adaptation from initial error ($E_0 + E_f$), observed during the first trials (figure 2.2, red trajectories) to the final error (E_f) that remains during the final trials (figure 2.2, green trajectories). Thus τ provides a measure of the speed of learning. Retention would be indicated by a faster error-reduction rate, and thus a smaller time constant τ, for relearning (second exposure) when compared to naive learning (first exposure).

With regard to the RI paradigm (figure 2.4a, b), both subject groups show a significantly smaller τ (p_{field} B = 0.01; p_{field} A = 0.02), thus faster relearning in the second exposure. The FI paradigm (figure 2.4c, d)

shows similar results (p_{field} B = 0.04; p_{field} A = 0.03) for both groups, with a smaller τ for the second than the first exposure. In contrast, regardless of paradigm type and subject group, the error on the first trial (represented by $E_0 + E_f$) did not differ between the first and second exposure, suggesting that subjects were naïve to the force environment switch in both cases. Additionally, the remaining error at the end of adaptation (represented by E_f) did not differ between first and second exposure, indicating that on the first exposure block subjects had reached full adaptation and that no further improvement occurred in the second block.

Figure 2.5 summarizes the results for all paradigms, plotting τ of the first exposure versus that of the second exposure, for each subject separately. Symbols indicate the different paradigms. The majority of points are below the identity line, showing that relearning is faster during the second exposure for most subjects.

Taking together, in contrast to previous work with body-stationary subjects interacting with robot generated force fields (Shadmehr and Mussa-Ivaldi, 1994; Brashers-Krug et al., 1996; Caithness et al., 2004), all our analyses show that subjects are able to retain a previously established internal model of force pairings induced by whole-body acceleration after being exposed to an interfering perturbation block. This observation holds regardless of force environment or interference level.

2.3.3 *Catch trials*

Finally, it is important to demonstrate that learning of an internal model occurred in our paradigms. The catch trials, in which the force was unexpectedly removed by not moving the sled during the reach, served this purpose. If an internal model is established, catch trials will show aftereffects due to the compensation for expected forces, which are not present. The more the subject has adapted to the new force environment, the greater the aftereffect in the catch trials (Shadmehr and Mussa-Ivaldi, 1994). Hence, to demonstrate learning, the size of the hand-path error in the catch trials should increase with the number of trials performed in a block. Figure 2.2 shows the trajectories of the interspersed catch trials,

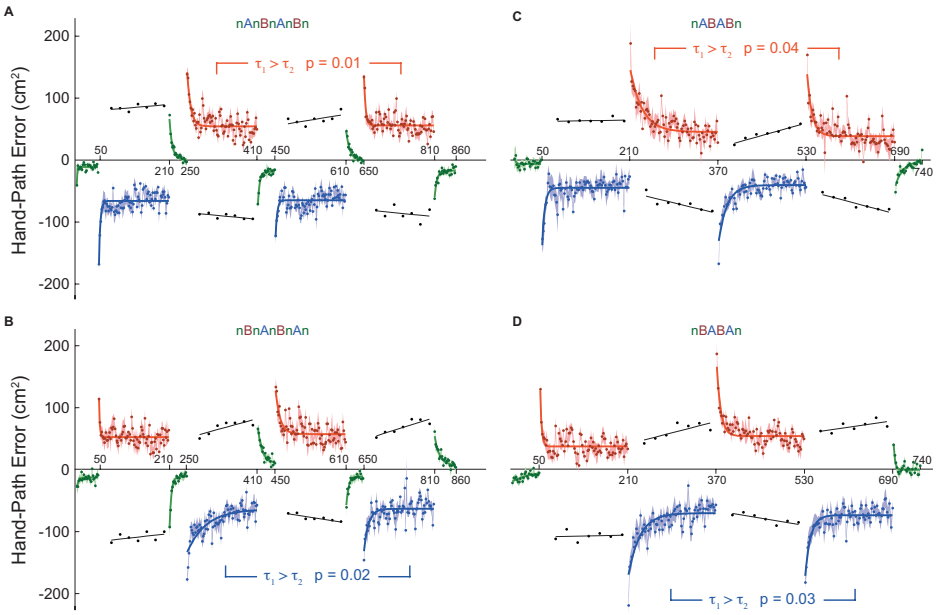


Figure 2.4: Hand-path error as a function of trial pair (dots), averaged across subjects. Shaded areas denote SE. A single rate exponential function (solid lines), fitted to the perturbation errors, suggests faster relearning at reexposure. Green, null trial; blue, force pairing A; red, force pairing B. Black dots represent catch trials, and black solid line presents their best fit line. *A: subject group 1.* Comparison of field B exposures (RI). *B: subject group 2.* Comparison of field A exposures (RI). *C: subject group 3.* Comparison of field B exposures (FI). *D: subject group 4.* Comparison of field A exposures (FI).

	1st Exposure *(Block 2)*		2nd Exposure *(Block 4)*		
	Mean	SE	Mean	SE	P Value
nAnBnAnBn					
$E_0 + E_f$	136.6	12.6	139.5	9.1	0.77
E_f	51.4	5.9	55.6	6.3	0.22
τ	10.9	5.4	1.9	0.5	0.01
nBnAnBnAn					
$E_0 + E_f$	-148.4	7.9	-138.6	5.9	0.36
E_f	-64.5	4.6	-59.6	4.2	0.19
τ	20.2	4.3	10.7	4.4	0.02
nABABn					
$E_0 + E_f$	170.4	21.3	156.2	17.4	0.46
E_f	34.6	7.9	34.5	13.4	0.99
τ	21.9	10.3	7.6	5.2	0.04
nBABAn					
$E_0 + E_f$	-202.2	13.9	-212.2	10.9	0.13
E_f	-64.1	6.2	-74.1	8.3	0.13
τ	15.6	6.7	4.9	1.1	0.03

Table 2.1: Mean and standard error values of exponential fit parameters. Values are means and SE of exponential fit parameters: $E_0 + E_f$ represents the error at the beginning of learning, in cm²; E_f is the offset representing the learning plateau, in cm²; and τ is the time constant of adaptation, in forward and backward pairs.

color-coded by trial number using a light-to-dark gray scale. They show increasing deviation from a straight line, in the direction opposite of the field trials, with progressing level of adaptation.

To quantify these deviations, the black data points in Figure 2.4, together with their fit lines, show the average E on the catch trials for each block and paradigm. The slope of the fit lines was not significantly different from zero ($p = 0.83$) across paradigms during the first perturbation block, indicating an overall lack of internal model formation. Once our subjects got more acquainted to our setup (blocks 2-4), E in the catch trials started to increase over the course of a perturbation block ($p < 0.001$). Because of the lack of internal model formation in the first perturbation block and because the immediate history of force environments is only

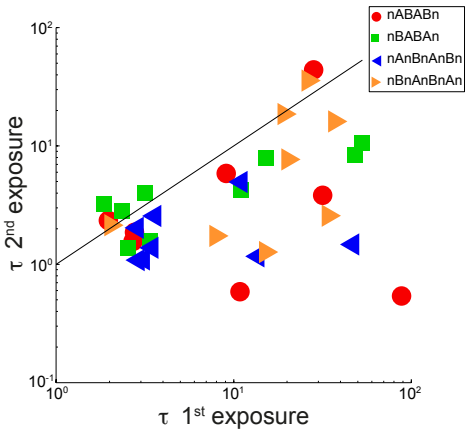


Figure 2.5: Time constants (τ) of the 1st exposure vs. time constants of the 2nd exposure of individual subjects.

equivalent for blocks 2 and 4, we only assessed our retention hypothesis for these blocks.

2.4 DISCUSSION

We studied the adaptation of reaching movements to two opposing dynamic environments, induced by whole-body accelerations on a vestibular platform. Our results show that subjects are able to retain and recall the learned dynamics during reaches after adapting their reaches to the opposing force environment. This result held even with full levels of anterograde and retrograde interference between the two force pairings. Our results suggest that the vestibular system, as part of the sensorimotor loop, disambiguates the force environment, allowing subjects to learn and readily recall two opposing force environments linked to the same movement goal. Furthermore, none of the subjects reported a switch in force pairings during the experiment, making an explicit strategy unlikely. We will next discuss the implications of our results.

Motor adaptation results in the formation of a memory that contains the control strategies (internal model) for reaching in the new environ-

ment. Previous work in body-stationary subjects learning force fields induced by robotic interfaces showed that the memory of a single force field can be retained, even when a period without a force field ("null-field") has intervened (*AnA* paradigm; Caithness et al. (2004)). However, when the null field is replaced by the opposite field of *A*, as tested in the *ABA* paradigm, the motor memory of *A* seems to have disappeared after the learning of field *B*. Even when static visual or haptic cues are provided to indicate the change in force fields, subjects fail to show task savings in the relearning of *A* (Gandolfo et al., 1996; Cothros et al., 2008). Only when the two opposing force fields are interspersed with a long delay (i.e. a day) or by extensive training (Krakauer et al., 2005), with random or frequent switches of fields, they can be learned (Osu et al., 2004).

While static visual and haptic cues may fail in supporting retention, our results suggest a role for vestibular cues in the independent formation and retrieval of multiple internal models or motor memories. The important difference compared to standard visual and haptic cues is that the vestibular system is an integral part of the sensorimotor loop, in that its signals are involved in online feedback control of the movement (Bresciani et al., 2005).

Recently, Howard et al. (2012) have shown that a dynamic visual cue is able to serve as contextual information, and reduce interference, if incorporated into the sensorimotor loop by dynamically timing and aligning it with the onset of the movement. Similarly, using two opposite visuomotor rotations, Hirashima and Nozaki (2012) trained subjects to physically perform the same movement in the context of two distinct visual targets (thus two motor plans). Next, they added two opposing curl force fields linked to the two motor plans and showed that subject could learn to compensate for the two fields without interference. In contrast to both studies (Hirashima and Nozaki, 2012; Howard et al., 2012), our study does not artificially create a connection between visual input and motor execution but makes use of the natural, direct link between the vestibular and motor system providing a cue within and not prior the execution of the reach. We show that this can also disambiguate two contexts, enabling the system to readily select the appropriate internal

model. The vestibular system directly senses the underlying accelerative cause of the perturbing forces, enabling immediate corrective responses and providing important information about the dynamic environment.

To our knowledge, we are the first to show the contribution of a vestibular cue to multiple task savings and recall in force environments. In the present study, subjects adapted to two opposite force environments, even though the visual context remained the same, i.e. the reach target was the same. In other words, two distinct internal models can be learned and retrieved while having only one movement intention. Thus, in our case, retention is not facilitated through a difference in the visual (Hirashima and Nozaki, 2012) or motor plan (Nozaki et al., 2006; Hwang et al., 2006a; Howard et al., 2010; Malone et al., 2011; Howard et al., 2008, 2012) but by contextual coupling of internal models through vestibular cues during task execution.

Although we attribute the retention effect to the vestibular input, the whole-body acceleration also activates cutaneous receptors due to the pressure and shear forces. We cannot dissociate their contribution from the vestibular contribution to retention (Clemens et al., 2011). In contrast, it is unlikely that proprioceptive signals have cued the opposing force environments. Previous studies have shown that when reach goal and initial limb configuration are the same, proprioceptive feedback signals throughout the reach do not induce retention. Therefore, in the current study, in which reach goal and limb configuration are the same for the force environments, other signals (i.e., vestibular and/or cutaneous sensory signals) have provided relevant contextual cues to distinguish the imposed force environments.

Why would proprioceptive error signals from a perturbed reach, that are essential for adaptation, fail to serve as contextual cues for learning two opposite perturbations (see e.g. Caithness et al., 2004). We suggest that the important difference with vestibular signals is that such time-varying proprioceptive signals represent a mixture of cause and effect. In contrast, vestibular signals solely reflect the cause of error but not the actual error signal itself. If the brain cannot dissociate the underlying causes of the errors (Berniker and Kording, 2008), it is also unable to attribute them to separate internal models. In contrast, time-varying pro-

prioceptive signals from a pre-cueing movement, i.e. movements prior to perturbation exposure (Howard et al., 2012), initial limb configuration (Nozaki et al., 2006), and movement intentions (Hirashima and Nozaki, 2012; Howard et al., 2010, 2008) do dissociate the two contexts and as a result two separate internal models are formed and retained.

Two theories have been proposed in the literature on the mechanism by which a contextual cue could enable savings. One theory suggests that memories can be in an active or inactive state. During the formation of a memory, the information is first coded in an active and readily available state. The memory can turn over to an inactive state when no further events occur on which the memory is based or if no further actions occur. An inactive memory needs to be reactivated to return to an active state if it is to be used in guiding behavior (Nader et al., 2000; Nader, 2003). It requires task-dependent contextual cues to decide when and which motor memory should be reactivated. If there are no such cues, the memory remains in the latest, active state, and is constantly modified, even if the dynamics of the environment change (Caithness et al., 2004). Recently this idea has been implemented in a model using multiple states that are operated by contextual cues (Lee and Schweighofer, 2009). Although this model is agnostic as to the nature of these contextual cues, here we suggest they must be task-related cues, of sensorimotor origin, to operate the switch.

A second theory is that in the learning of field *A*, followed by the learning of field *B*, two distinct memories are formed. The memory of *A* is not modified by *B*. Instead, both memories co-exist but the most recently stored memory masks the other. This explains why in the *ABA* paradigm there is no faster relearning at re-exposure of field *A*, when no task-dependent contextual cues are provided. In other words, this theory suggests that multiple motor memories are encoded, but the retrieval of the correct memory for a specific task requires task-dependent contextual cues. Behaviorally, both theories yield the same outcome: no faster relearning at re-exposure of field *A* in an *ABA* paradigm, in the absence of contextual cues (Pekny et al., 2011; Criscimagna-Hemminger and Shadmehr, 2008).

In both the RI and FI paradigm, contextual cues mediate switching between motor memories by activating or unmasking them. The result is observed as savings. It has been suggested that savings are improved if anterograde interference is reduced by the use of washout trials (Miall et al., 2004). However, our data showed retention both when anterograde inference is minimized (RI paradigm, using intervening washout trials) and when there are full levels of anterograde and retrograde interference (FI paradigm). In both paradigms, learning took place significantly faster during the second exposure to the same force pairing compared to the first exposure (see figures 2.2-2.4), suggesting that the vestibular cue distinguishes among fields *A*, *B* and null.

To our knowledge, there are no reports that tested reach adaptation to inertial forces induced by linear whole-body accelerations. Changes in control strategies in response to perturbation of gravitational forces, through micro- or hyper gravity, have been reported (Crevecoeur et al., 2009, 2010). In those experiments vestibular signals certainly play a role, but have not tested retention in terms of an *ABA* paradigm. In other previous literature, adaptation to Coriolis forces has been studied while reaching during constant-speed body rotations (Lackner and Dizio, 1998). However, in such experiments the vestibular system no longer indicates movement. Also in Hwang et al. (2006a) the vestibular system was not involved, since they studied reaches in the presence of inertial forces created by a haptic manipulandum. They found that the trajectories of the adapted reaches did not converge to straight movements, but curved 1 to 2 cm away from a straight line. We made similar observations in our paradigm (see figure 3.2). These findings do not imply that adaptation was incomplete. The view that adaptation is about canceling kinematic effects of a perturbation, thus that movements return to near baseline (unperturbed) conditions (e.g. a straight line), has recently been challenged by Izawa et al. (2008). They suggest that motor adaptation is a process of reoptimization, possibly resulting in a different trajectory in the new environment (Chib et al., 2006; Izawa et al., 2008). Our results support this notion. Subjects exploited the force field by using a control policy that initially counteracts the inertial forces im-

posed by the accelerating body and after the hand had reached peak velocity use the body's deceleration to pull the hand back to target.

Finally, we note the difference between the observed learning rates when using a haptic manipulandum (Shadmehr and Mussa-Ivaldi, 1994) compared to using a rotating room (Lackner and Dizio, 1998) or linear accelerations to introduce a force field. In the first setup, in which there are contact forces on the reaching hand, subjects need about 80 trials to reach a stable state. When there are no contact forces, as in the latter two setups, learning seems to occur about twice as fast, suggesting that contact-free inertial forces acting on the entire arm are taken into account more readily than contact forces acting on a single point.

Taking all findings into account, we suggest that the vestibular system plays an important role in coding and decoding multiple motor memories. This system provides information about the environmental dynamic changes and a strong contextual cue for different types of force fields. Such cues, if an integral part of the sensorimotor loop, substantially reduce interference and improve the formation and selection of multiple memories.

2

3

GENERALIZATION AND TRANSFER OF CONTEXTUAL CUES IN MOTOR LEARNING

Adapted from:
Sarwary AME; Stegeman DF; Selen LPJ; Medendorp WP (2015). *Generalization and transfer of contextual cues in motor learning*, Journal of Neurophysiology:jn.00217.2015

3.1 INTRODUCTION

Our brain is able to adapt our movements to changes in the dynamics of our body and environment by building and adjusting internal models, thought to be formed by changes to motor primitives (Thoroughman and Shadmehr, 2000; Donchin et al., 2003; Poggio and Bizzi, 2004). These changes cause that an internal model for reaching, acquired at a specific movement direction, not only guides movements in that direction but also generalizes to neighboring movements (Mattar and Ostry, 2010; Izawa et al., 2012). The extent of this generalization reduces as a function of the angular separation from the trained movement direction.

If multiple internal models are learned for the same movement direction the same set of motor primitives will be involved in the adaptation. This typically causes interference between representations, slowing down or even abolishing learning of the internal models (Caithness et al., 2004).

Contextual cues are known to reduce this interference. Multiple internal models can be learned and recalled in parallel if each of them is uniquely linked to a contextual cue, like wrist posture (Gandolfo et al., 1996), a visuomotor association (Hirashima and Nozaki, 2012), a pre-movement (Howard et al., 2012), or vestibular input (Sarwary et al., 2013).

If multiple internal models can be learned based on contextual cues, how does the brain generalize across these cue representations ('cues' for short)? Analogous to the generalization of an internal model around the trained movement direction, cue-related internal models could also show generalization around the trained cue dimension. If so, one would predict that in a paradigm where two distinct contextual cues are linked to two distinct internal models, the net generalization represents the combined effect of the two single cues' generalization profiles. In support, Ghahramani and Wolpert (1997) reported that when subjects learn two starting-point dependent visuomotor mappings, the generalization of this learning to untrained starting points can be described by a mixture of the two learned maps. The first objective of this study is to test cue-based generalization in human subjects adapting their reaches to

two opposite curl force fields each associated with their own contextual pre-movement cue (Howard et al., 2012).

An internal model acquired for reaching with one hand does not only generalize within that hand, but also generalizes to the untrained hand. This transfer is only about 10% (Joiner et al., 2013), with ongoing debate on whether it takes place in extrinsic (Dizio and Lackner, 1995; Criscimagna-Hemminger et al., 2003) or intrinsic coordinates (Wang and Sainburg, 2004; Galea et al., 2007). Following from this notion, our second objective is to test whether and if so, in which reference frame, the cue-related generalization transfers to the un-trained hand.

Our subjects made two-stage reaching movements (figure 3.1): The first movement served as a contextual cue for the perturbing forces in the second movement (Howard et al., 2012). Two pre-movement directions were uniquely coupled with opposite force fields. After adaptation, we quantified generalization around the trained pre-movement directions and transfer of this generalization pattern to the untrained hand. In a second experiment we focused on interference between the two cue-related internal models by changing the relative strength of the associated force fields. In a third experiment we determined the generalization pattern around a single association between a pre-movement cue and force field.

We show that generalization of the contextual pre-movement cue follows Gaussian-like decay around the trained direction. Individual cue generalizations interfere at intermediate directions, as revealed by a mixed expression of the two associated internal models. Furthermore, cue-related generalization transfers to the untrained hand in an extrinsic frame of reference, irrespective of whether learning was performed with the dominant or non-dominant hand.

3.2 MATERIALS AND METHODS

3.2.1 *Participants*

Experiments were conducted under the general approval for behavioral experiments by the institutional ethics committee. In total 40 (30 female)

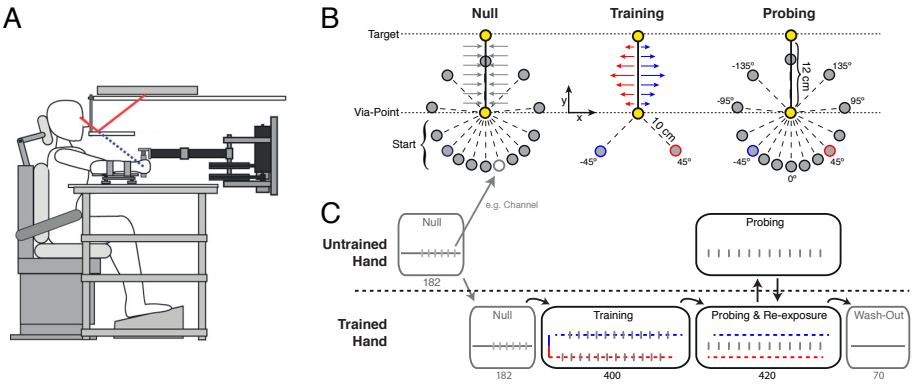


Figure 3.1: Experimental design. *A:* Setup: Subjects were seated in front of a robotic rig performing reaches holding the handle of a planar robotic manipulandum (vBot). Both arms were resting on air sleds floating on a glass top table. Courtesy of Franklin and Wolpert (2008). *B:* Task: Reaches were performed starting with a pre-movement from start position to via-point. This was followed by a movement from via-point to target. The three panels show the pre-movement directions and perturbation couplings used within the null, training, and probing block. *C:* Paradigm. Illustration of the force field schedule within each block. Vertical grey bars denote error-clamp trials.

naive subjects between 18 and 28 years of age (mean = 23.4, SD = 3.0) gave their written consent to participate in the experiments. Reimbursement was provided in terms of payment. All subjects had normal, or corrected-to-normal vision and had no known motor deficits. All subjects were right-hand dominant with a laterality index of 100 according to the Edinburgh test of handedness (Oldfield, 1971).

3.2.2 *Apparatus and setup*

Subjects were seated on a height adjustable chair in front of a robotic rig (figure 3.1A). Both their right and left arm rested on air sleds floating on a glass top table. Reaches were performed while holding the handle of

a planar robotic manipulandum, vBot (Howard et al., 2009). The vBot in combination with the air sled only allows movement in the horizontal plane and measures position and generates forces at the handle that are updated at 1000 Hz. Stimuli were presented within the plane of movement via a semi-silvered mirror, reflecting the display of a LCD monitor suspended horizontally above (figure 3.1A). This configuration also allowed visual feedback of hand position to be overlaid into the plane of the movement. Subjects were prevented from viewing their arm directly. Start position, via-point, and target position were presented as circles of 1.5 cm radius. Current hand position was represented by a red circle of 0.5 cm radius.

3.2.3 *Reach task*

Subjects had to perform reaching movements consisting of two stages. The first stage was an unperturbed contextual pre-movement (10 cm amplitude) from the start position to the via-point. The second stage was a target-directed movement from the via-point to the target position (12 cm amplitude). At the beginning of a trial, start position (in grey), via-point (in yellow) and target position (in yellow) were simultaneously displayed.

Contextual pre-movement: Before the start of a trial the subject had to place the hand cursor within the start position and stay still (cursor speed < 5cm/s for 100msec). Then, a tone instructed to start the contextual pre-movement reach. If the reach was initiated before the tone or started >1s after the tone, an error message appeared on the screen ('wait for beep' or 'move after beep') and the trial was repeated. If the pre-movement ceased at the via-point with a speed < 5cm/s, the via-point turned green and a second tone signaled to continue the reach towards the target. If subjects did not stop their movement at the via-point, or the pre-movement had a duration > 500msec, an error message was displayed on the screen ('stop at via-point' or 'move faster') and the trial was repeated. During the pre-movement stage of the reach the vBot's motors were always turned off.

Targeted movement: The start of the targeted movement was defined as the first point where the hand speed was > 5 cm/s after the second tone. If subjects did not initiate the targeted movement within 400msec after the second tone, an error message was given ('move after second beep') and the trial was repeated. The endpoint of the targeted movement was defined as the first point where the speed < 5cm/s. If this endpoint was within the target position, the target turned from yellow to green. If the endpoint was not within the target position a feedback message was given ('stop at target'). If the endpoint was within the target position, but the movement duration was > 500msec a 'move faster' feedback message was given. These feedback messages were used to make the reaches more consistent, but did not lead to rejection of the trial.

During the targeted movement the motors could be off (null), produce a curl force field (clockwise or counterclockwise) or produce an error clamp (Scheidt et al., 2000; Smith et al., 2006).

A curl force field produces forces that are perpendicular to movement direction and proportional to the reach velocity:

$$\begin{bmatrix} F_x \\ F_y \end{bmatrix} = b \begin{bmatrix} 0 & -1 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} \tag{3.1}$$

in which the damping constant b was set to +13 and -13 Ns/m (equal strength CW and CCW force fields), or to +16 and -8 Ns/m (unequal strength CW and CCW force fields, respectively). The sign of b thus determined the direction of the force field (CW or CCW) and was uniquely coupled to a contextual pre-movement direction.

Error-clamp trials constrain the movement onto a straight line from the start to the target position. The hand was constrained to a straight path using a spring constant of 6,000 N/m and a damping constant of 7.5 Ns/m. Both the curl force fields and error clamps were initiated at the onset of the second tone, from which damping and spring constants were linearly ramped up over 50 msec to avoid instabilities due to discontinuities in the forces.

3.2.4 *Experiment 1: equal strength force fields*

Two groups of 8 subjects performed the reach task. One group learned to compensate for the cued force fields with their dominant (i.e. right) hand and the other group learned this with their non-dominant (i.e. left) hand. Start positions for the pre-movements were defined on a 10 cm radius circle centered around the via-point. A total of 14 pre-movement directions (-135, -95, -65, -45, -30, -15, 0, 15, 30, 45, 65, 95, 135, 180 degree) were defined on this circle (figure 3.1B). Only the -45° and 45° pre-movement directions were linked to a force field in the subsequent targeted movement. This 12cm targeted movement was always in the mid-sagittal plane, for both the right and left hand.

Subjects started an experimental session using the untrained hand. With this hand they performed 182 null trials (13 batches of the 14 pre-movement cues) to get accustomed to the passive robot dynamics and the experimental constraints. In each batch the 14 pre-movement cues were presented in random order. Within these 13 batches, each pre-movement direction was randomly probed 5 times with an error-clamp to assess baseline force expression during the targeted movement.

The same 182 null trials were repeated with the opposite hand, i.e. the hand that would subsequently learn the associations between the two pre-movement cues and force fields.

After having established the baseline performance for each hand, a block of 400 adaptation trials followed (group 1: right hand; group 2: left hand), in which subjects learned the pre-movement cue to force field associations. The pre-movements were made from the -45° and 45° start positions (figure 3.1B), which provided a unique cue to the force field of the subsequent targeted movement (-45° pre-movement cued the CW field; 45° pre-movement: cued the CCW field). The two pre-movement cues were presented pseudo randomly, such that a batch of 10 trials contained 4 CW trials, 4 CCW trials and 2 error-clamp trials, one for each pre-movement cue. The error clamp trials measured the degree of adaptation to each cued force field.

Subsequently, the generalization of the force fields in relation to the two pre-movement cues was probed, by testing the force expression in

the trained and untrained hand for all 14 pre-movement directions using error-clamps. Probe trials were mixed with re-exposure trials to keep adaptation at asymptotic level. Re-exposure trials were applied to the originally trained hand for the two trained pre-movement cues and their respective force fields (figure 3.1B). In each batch of 6 trials, the 3rd trial was an error clamp trial with the untrained hand, the 6th an error clamp trial with the trained hand, and the remaining four trials were re-exposure trials to the trained hand. A message in the workspace display indicated the hand switches. Both hands were supported by their own air sled and the subject only needed to change the hand that grasped the handle of the vBOT. All fourteen pre-movement directions were probed 5 times in each hand, resulting in a total of 420 trials (6 *14 * 5).

Finally, the session ended with a wash-out block of 70 trials, entailing reaches with the trained hand in all possible pre-movement directions, each presented 5 times in random order.

3.2.5 *Experiment 2: unequal strength force fields*

In a second experiment we examined in further detail the interference between the two cue-related internal models. To this end, 8 new subjects performed our cued reaching task, but now the opposite force fields had unequal strengths. This experiment was similar to experiment 1, however we only trained and probed generalization of the dominant right hand. Subjects were exposed to one null block (182 trials), an adaptation block (400 trials), a probing block (140 trials) and a washout block (70 null trials). During the probing block all 14 cue angles (same as in experiment 1) were probed 5 times. Re-exposure trials were mixed in with error-clamp trials such that every second trial was a re-exposure trial.

3.2.6 *Experiment 3: single pre-movement cue*

In a third experiment, we investigated whether the simultaneously observed generalization patterns of two cue representations relate to the generalization of a single cue after having learnt a single force field. We

tested 16 right-hand subjects, divided in two groups, using right-hand reaching movements. One group (n=8) had the -45° pre-movement cue coupled with a clockwise force field; the other group had the 45° cue coupled to a counter clockwise force field (field strengths as in exp 1). Subjects were exposed to one null block (182 trials), an adaptation block (200 trials), a probing block (140 trials) and a washout block (70 null trials). All 14 cue angles (same as in experiment 1) were probed 5 times during the probing block. Every second trial of the probing block was a re-exposure trial.

3.2.7 *Analyses*

Data were stored for offline analysis in MATLAB (The MathWorks). Kinematics and dynamics of the targeted movement were the main focus of the analyses. For completeness, we also analyzed the kinematics of pre-movements to assure that kinematic differences between the cue movements cannot drive our effects.

Start (t_0) and endpoint (t_f) of the targeted movement was determined based on a speed threshold of 5 cm/s. In all but the error clamp trials, deviation of the movement trajectory from a straight line was calculated using the signed hand-path error (E) defined as:

$$E = \int_{t_0}^{t_f} x(t) \cdot \dot{y}(t) dt \tag{3.2}$$

where x(t) is the perpendicular distance of the actual trajectory compared to a straight line joining start position at the via-point and target position and $\dot{y}$(t) is the hand velocity in the direction of the target (Franklin et al., 2003).

From the error-clamp trials, we computed an adaptation index (AI) representing the degree of force compensation to the curl-force field. For each trial, the theoretical time-varying force generated by the curl field was calculated based on actual hand velocity. This theoretical force was regressed against the force measured in the error-clamp, providing

a regression coefficient in the range of -1 to 1 (Smith et al., 2006). The sign was introduced to separate the compensatory forces for the CW and CCW curl fields. Adaptation indices were baseline corrected by subtracting for each pre-movement direction the mean AI derived in the null trials, recorded in the beginning of the paradigm. In the analyses of experiment 2 we regressed the force expression against the theoretical forces of the strongest force field. As a result, perfect compensation for the weaker force field would result in an AI of 0.5.

To assess learning during the adaptation block we looked at kinematic (E) and dynamic (AI) learning parameters. We used paired t-tests comparing the average of the initial 5 versus final 5 hand-path errors and the average of first 2 versus last 2 AI. To check whether adaptation levels remained at an asymptotic level during the generalization block, we performed ANOVAs with E or AI as dependent variables.

3.2.7.1 *Learning rates*

To quantify learning rate in the adaptation blocks, we fitted a single-rate exponential function to the pattern of the hand-path error:

$$E(n) = E_0 \cdot e^{-\frac{n}{\tau}} + E_f \tag{3.3}$$

in which $E_0 + E_f$ represent the error at the first trial, τ the time constant (in trials) of adaptation and E_f the asymptote error, and n trial number. As two internal models (CW and CCW) were learned simultaneously, we flipped the sign of the 45° cue HPEs and collapsed the data of the opposite field before performing an exponential fit. We used confidence intervals assessed via bootstrapping (1000) to compare exponential fit values of dominant hand and non-dominant hand training.

3.2.7.2 *Generalization curves*

During the adaptation block, the two opposite force fields were trained simultaneously with -45° and 45° pre-movement cue directions. To infer the generalization around the pre-movement cues, we assumed the force expressed during the targeted movement, as measured by AI, to fall-off

in a Gaussian fashion with angular deviation of the pre-movement from the trained direction. Because each cue is associated with its own internal model, the observed cue generalization curve was regarded as a net expression of two cue-based internal model representations. As a result, we modeled the generalization of the trained cues as two overlapping Gaussian shaped functions, both centered at their trained pre-movement direction (-45° and 45°):

$$AI(c) = A_{-45} \cdot exp(-\frac{(c - c_{-45})^2}{2\sigma_{-45}^2}) + A_{45} \cdot exp(-\frac{(c - c_{45})^2}{2\sigma_{45}^2}) + B \quad (3.4)$$

in which c represents pre-movement direction, with c_{-45} and c_{45} referring to the trained directions. The model contains 5 free parameters: two gain factors A_{-45} and A_{45}, that represent the force expression at the two trained cue angles, two width parameters σ_{-45} and σ_{45}, that represent the angular extent of generalization around the trained cue angles, and an overall offset term B. This model was fit independently to the AI data from the trained and untrained hand. Statistical differences between model-parameters for the trained and untrained hand were assessed using t-tests.

The model was then used to make predictions for the interference levels between internal models of unequal strength in experiment 2. These predictions were based on σ set to the combined average of σ_{-45} and σ_{45} across all subjects obtained from experiment 1. The offset (B) parameter was set to 0, and the gain parameters A_{-45} and A_{45}, stemmed from the behavioral data of experiment 2, by averaging the final 6 AIs of the -45 and 45 degree cue on an individual subject basis. We also fitted the model to the individual subjects' data with 4 free parameters (A_{-45}, A_{45}, B, and $\sigma_{-45} = \sigma_{45}$) and then compared the fitted parameters to the parameters we used to make predictions using t-tests.

Finally, a similar, but reduced model was used to fit the data of experiment 3, in which the generalization of a single cue in relation to a single-force field was investigated. Therefore, the model contained only a single Gaussian shaped function centered at the trained pre-movement direction in combination with an offset term.

3.3 RESULTS

We performed three experiments. In the first experiment, subjects learned to compensate for two opposite force fields of equal strengths, each cued by a unique pre-movement direction (-45° or 45°). After learning we probed the spatial generalization of these pre-movement cues in the trained hand and their transfer to the untrained hand. In the second experiment, subjects also learned two cue-related (-45° and 45°) opposite force fields, but now of unequal strength. This should result in different interference levels of pre-movement cues. We used a cue-based generalization model to interpret generalization of both the equal and unequal strength force field representations. The validity of this model was further investigated in a third experiment in which we quantified generalization around a single cue in relation to a single-force field.

We start with the description of the results of the first experiment in which one group trained with their dominant (right) hand and another group with their non-dominant (left) hand (figure 3.1B). After both force fields had been learned, the force expression during the targeted movement was measured for untrained pre-movement directions, for both the trained and untrained hand (figure 3.1C).

3.3.1 *Simultaneous learning of two internal models*

Both the dominant and non-dominant hand training group learned to compensate for the CW and CCW force field. Figures 3.2A and 3.2B show the evolution of the hand-path error over the adaptation and generalization phase of the experiment for training with the dominant and non-dominant hand, respectively. Both groups show adaptation to the two force fields, which was verified by a significant decrease in hand-path error from the first 5 to the last 5 trials of the adaptation block (each $p < 0.001$). This observation was corroborated by a significant increase in AI, a measure of the compensatory force into the error clamps, over the course of the adaptation (first two versus last two trials; each $p < 0.001$) for both force fields and subject groups (figure 3.2C and 3.2D).

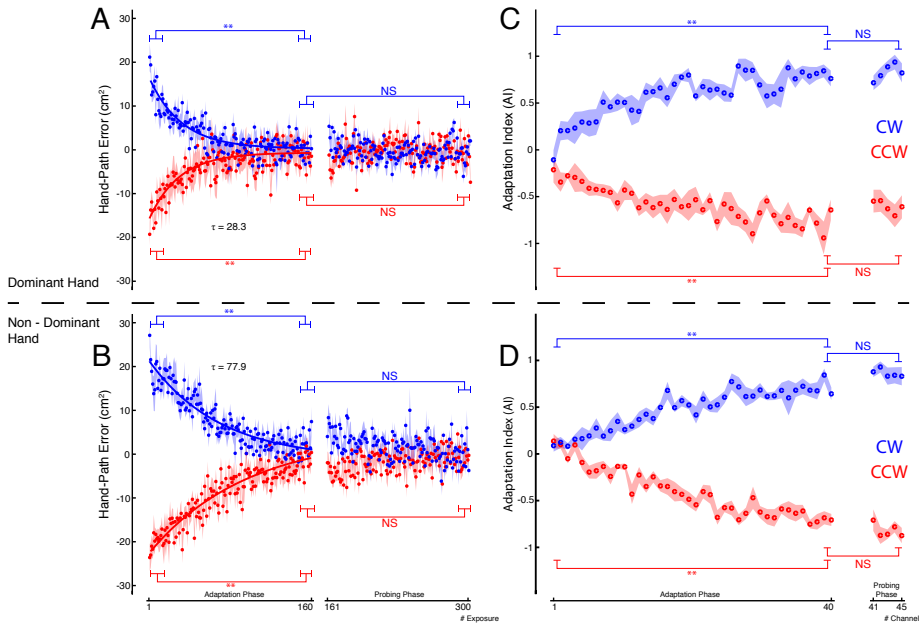


Figure 3.2: Hand-path error (left panels) and Adaptation Index (right panels) during adaptation and probing phases of the paradigm, averaged across subjects. Shaded areas denote SE. Top row, dominant hand trained, bottom row, non-dominant hand trained. Blue: clockwise force field (CW). Red: counterclockwise force field (CCW).

Figure 3.2 also suggests that the non-dominant hand is slower in learning to compensate for the force fields. To quantify this, we fitted a single rate exponential function to the hand-path error (Eq. 3.3, see Methods). For this analysis we collapsed the data of the two cues (-45° and 45°) after changing the sign of the force expression from the 45° cue. The exponential function represents the speed of learning by the parameter τ. Comparing the τ values across groups based on 1000 bootstraps, the dominant hand (τ = 28.3 trials, 95% CI [13.5 43.1]) learns significantly faster than the non-dominant hand (τ = 76.7 trials, 95% CI [55.5 97.9]).

The paradigm was designed such that the level of adaptation, as obtained at the end of the adaptation phase, should remain unchanged dur-

ing the subsequent block that probes generalization. Figure 3.2 shows *E* and AI for the trained cue locations for the trained hand during the probing phase of the paradigm, which both remain virtually constant. To substantiate this observation, we performed a 3 way ANOVA on *E* and AI with the factors block (adaptation, probing), pre-movement direction (-45°, 45°) and hand (dominant, non-dominant). When comparing *E* averaged across the final 15 trials of the adaptation versus probing phase, there was no significant effect of block ($F_{(1,57)}$=0.09; p=0.77), pre-movement direction ($F_{(1,57)}$ < 0.001; p=0.99), or hand ($F_{(1,57)}$=0.03; p=0.87), or any of their interactions (each p > 0.26). Likewise, comparing AI (taking the mean of the final 2 trials of each phase), revealed no significant effects of block ($F_{(1,57)}$=0.02; p=0.88), pre-movement direction ($F_{(1,57)}$=0.15; p=0.7), or hand ($F_{(1,57)}$=0.05; p=0.83), or their interactions (each p > 0.66). Together, this indicates that adaptation levels indeed remained unchanged during the probing phase, a prerequisite to be able to probe reliably the generalization of pre-movement cue representations.

3.3.2 *Generalization of pre-movement cue representations*

Our data hitherto show that two internal models of reach dynamics are formed simultaneously, each contextually associated with a distinct pre-movement cue (-45° or 45°). The next question is whether and how these pre-movement cue representations generalize to untrained pre-movement directions.

Figure 3.3 shows the adaptation indices as determined during the error clamp trials of the probing phase, plotted as a function of pre-movement direction. Data are organized separately for the two groups (figure 3.3A: training of dominant, right hand; figure 3.3B, training of non-dominant, left hand). Both panels show clear generalization of context within the trained hand, i.e. the force expression during the targeted movement depends on the direction of the pre-movement. The fall-off in force expression, as measured by AI, seems steeper in between the two trained pre-movement directions (between -45° and 45° pre-movement directions) than for pre-movement directions outside this range ($|\text{direction}| > 45°$).

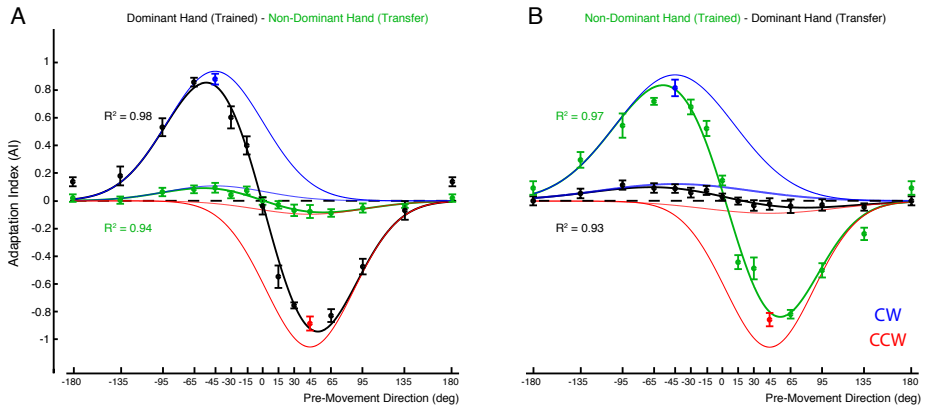


Figure 3.3: Adaptation Index as a function of pre-movement direction. *A:* Dominant hand training to non-dominant hand transfer. *B:* Non-dominant hand training to dominant hand transfer. Error bars denote SE. Red and blue dots represent force field trained at pre-movement directions. The Gaussian fits are superimposed: black (dominant hand), green (non-dominant hand). The model-based generalization curves of the single cues are plotted in blue and red, respectively.

Furthermore, figure 3.3 illustrates that the generalization effects of the pre-movement representations, as seen in the trained hand, transfer to the untrained hand, irrespective of whether the dominant (right) or non-dominant (left) hand was trained. Next we will analyze these data in more detail, first for generalization in the trained hand and then for transfer of this generalization to the untrained hand.

3.3.3 *Generalization of context in the trained hand*

To quantify the generalization results within the trained hand, we fitted two superimposing Gaussians (see Methods, Eq 3.4), centered at -45° (blue) and 45° (red) pre-movement directions, in terms of gain (A) and width (σ). The fitted net generalization curves (black and green) are overlaid onto the data points, yielding R^2 values of 0.98 ($p<0.001$) for the

dominant (black) and 0.97 ($p<0.001$) for the non-dominant hand (green), respectively. From the underlying representations (blue and red), it can now be clearly seen that their overlap explains the steep fall-off at the intermediate pre-movement direction ($\approx 0^{o}$).

The gain values (A_{-45} and A_{45}) indicate the fraction of compensatory force at the trained cue locations, which are comparable to the asymptotic AI values at the end of learning. They are significantly different from zero ($p < 0.001$) for both the dominant hand (A_{-45} = 1.12, SE = 0.05; A_{45} = -0.92, SE = 0.05) and the non-dominant hand (A_{-45} = 1.06, SE = 0.08; A_{45} = -0.96, SE = 0.05).

The widths of the Gaussians, characterizing the generalization curve of the cue representation, range from 39 to 57 degrees. The width of the Gaussians, associated with the -45° and 45° cue, are not significantly different (dominant: σ_{-45} = 40°, SE = 2°; σ_{45} = 47°, SE = 4°; p = 0.13; non-dominant: σ_{-45} = 57°, SE = 5°; σ_{45} = 44°, SE = 4°; p = 0.12). Therefore, we collapsed σ_{-45} and σ_{45} for each subject before comparing the extent of cue generalization in the dominant and non-dominant hand training groups. The non-dominant hand shows a significantly (p = 0.01) broader generalization for a single pre-movement cue ($\sigma_{non-dominant}$ = 51°, SE = 2°) than the dominant hand ($\sigma_{dominant}$ = 43°, SE = 2°). This difference can also be observed in figure 3.3, comparing the underlying representations (blue and red) across the trained hands (figure 3.3A versus 3.3B). The offset term B was not significantly different from zero (p = 0.07).

3.3.4 *Context transfers to untrained hand*

The next question to be addressed with experiment 1 was whether the observed generalization pattern in the trained hand also transfers to the untrained hand. Apart from the generalization within the trained hand, Figure 3.3 also shows the transfer of generalization of pre-movement cue representations to the untrained hand. Using the same Gaussian mixture modeling approach as for the trained hand, we quantified the force expression in the non-trained hand. There is clear transfer from the trained dominant to the untrained non-dominant hand as indicated by

the force expression, quantified by A, being significantly different from zero for both cues (A_{-45} = 0.11, SE = 0.03; A_{45} = -0.14, SE = 0.03; p_{-45} = 0.02, p_{45}=0.002). Both cue representations also show the same amount of transfer to the untrained hand (~10%, p = 0.45). There is also significant transfer from the trained non-dominant to the untrained dominant hand (A_{-45} = 0.13, SE = 0.02; A_{45} = -0.12, SE = 0.02; p_{-45} = 0.001, p_{45} < 0.001). Again, the two cue representations are similar in the amount of transfer (~10%) (p = 0.65).

The width of the fitted Gaussians for the -45° and 45° pre-movement cues do not differ in the untrained hand. Neither in the dominant to non-dominant hand transfer group (figure 3.3A, σ_{-45} = 46°, SE = 13°; σ_{45} = 48°, SE = 9°; p = 0.9) nor the non-dominant to dominant hand transfer group (figure 3.3B, σ_{-45} = 66°, SE = 13°; σ_{45} = 59°, SE = 11°; p = 0.63). The offset B is also not significantly different from zero (p = 0.2).

Finally, we asked in which reference frame this transfer took place. An intrinsic reference frame would suggest that the pattern of cue generalization of the trained hand is mirrored along the mid-sagittal plane, i.e. around the 0 degree direction, in the transfer to the untrained hand. Transfer in an extrinsic reference frame would entail that the same, non-mirrored, pattern of generalization would be observed in the untrained hand. Figure 3.3 clearly indicates the latter, suggesting that transfer of the pre-movement cue representations across hands occurs in an extrinsic reference frame.

3.3.5 *Interference between contexts: force fields of unequal strength*

Thus far, we showed that the pattern of generalization observed in experiment 1 is consistent with a model in which motor output is the weighted sum of separate internal models of the CW and CCW fields. The contribution of each internal model is weighted by a separate Gaussian function, which is tuned to the direction of the contextual pre-movement. At intermediate pre-movement directions this results in interference between representations. To further test this model, we performed an additional experiment (experiment 2), testing generalization and interference

of cued internal models associated with unequal field strengths (CW = 2*CCW). The prediction is that the increased output from the internal model associated with the CW field should skew the context-dependent pattern of generalization towards the CW cue direction.

Figure 3.4A shows that subjects can learn two force fields of unequal strength based on pre-movement cues. The hand-path error (figure 3.4A) demonstrates a significant decrease over the course of trials (both $p<0.001$), which was complemented by a significant increase of the AI (both $p<0.01$). A 2-way ANOVA on E (averaged across the final 15 trials of each phase) revealed no differences between adaptation and probing blocks ($F_{(1,28)}=4.25$; $p=0.29$), or between the two pre-movement directions ($F_{(1,28)} = 54.98$; $p=0.09$). The interaction between the two factors was also not significant ($F_{(1,28)}=0.03$; $p=0.87$). The 2-way ANOVA results of the AI (taking the mean of the final 2 trials of the adaptation and probing block), revealed no significant difference between the adaptation and probing block ($F_{(1,31)}=18.95$; $p=0.14$) either. However, there was a significant effect of pre-movement direction ($F_{(1,31)}=5936$; $p=0.008$) on the magnitude of the AI, caused by the different force field strengths. The interaction of block $\times$ pre-movement is not significant ($F_{(1,31)}=0.004$; $p=0.95$), confirming that adaptation levels remained constant throughout the probing phase for both force fields.

The results from experiment 1 were interpreted in terms of a mixture of two Gaussian shaped generalization curves. Based on the parameters of this model we made predictions for experiment 2 based on Eq 3.4. The σ_{-45} and σ_{45} values, obtained independently in experiment 1, did not show a significant difference and were therefore set to their combined average of $\sigma_{dominant}$ (43^{o}). The offset parameter B of Eq 3.4 was set to 0 for each subject. Gain parameters were derived from the individual subject data, taken as the average of the final 6 AIs for each cue separately on an individual subject basis.

In addition, we fitted the model from Eq 3.4 leaving all parameters free ($\sigma_{45} = \sigma_{45}$, A_{45}, A_{-45} and B) on an individual subject basis. Figure 3.4C shows the model prediction (solid lines) and model fit (dotted black line) based on the group average. The prediction ($R^2=0.95$) and the model fit ($R^2=0.96$) match closely. Figure 3.4D shows the model predictions with

data points (black circles) for the individual subjects. The data points closely match with the prediction of the model, with correlations that have R^2 values > 0.84 (each $p<0.001$).

However, it is important to point out that our behavioral data represents the net generalization output. The values of A_{-45} and A_{45} that we used to make predictions were based on the net generalization output and do not necessarily represent the true gain of the underlying cue generalization curves. This explains why the model underestimates the net AI for the 45° cue in figure 3.4C. We can also not rule out changes of σ and B in experiment 2. Therefore we also fitted the 4 parameter model and compared the fitted values to the values we used to make predictions.

The σ and B parameters are not significantly different between the prediction and the model fits ($p_\sigma = 0.48$, $p_B = 0.26$). The A_{-45} gain also shows no significant difference ($p = 0.98$). However, as expected from figure 3.4C, the A_{45} values directly derived from the AIs are significantly different from those of the model fits ($p = 0.03$). This confirms that the underlying representation of the force field obtained at the 45° cue is stronger than suggested by the net generalization curve. This can be explained by the interference of the stronger representation for the -45° cue representation.

Further support for altered levels of interference between cues that represent unequal strength force fields is provided by the angular shift of the zero crossing of the AI. Based on the model, the zero AI crossing point is not at 0° anymore (like in experiment 1), but is now shifted towards the 45° cue, which represents the weaker force field. This is also confirmed in the AI data where the AI amplitude of the -15° cue is significantly larger than the AI amplitude of the +15° cue ($p = 0.008$, $AI_{-15°} = 0.49$, SE = 0.07 and $AI_{15°} = -0.17$, SE = 0.04).

Taken together, the results from the prediction, model fit and raw data further validate the cue-based weighted contribution of the two internal models that we proposed in experiment 1.

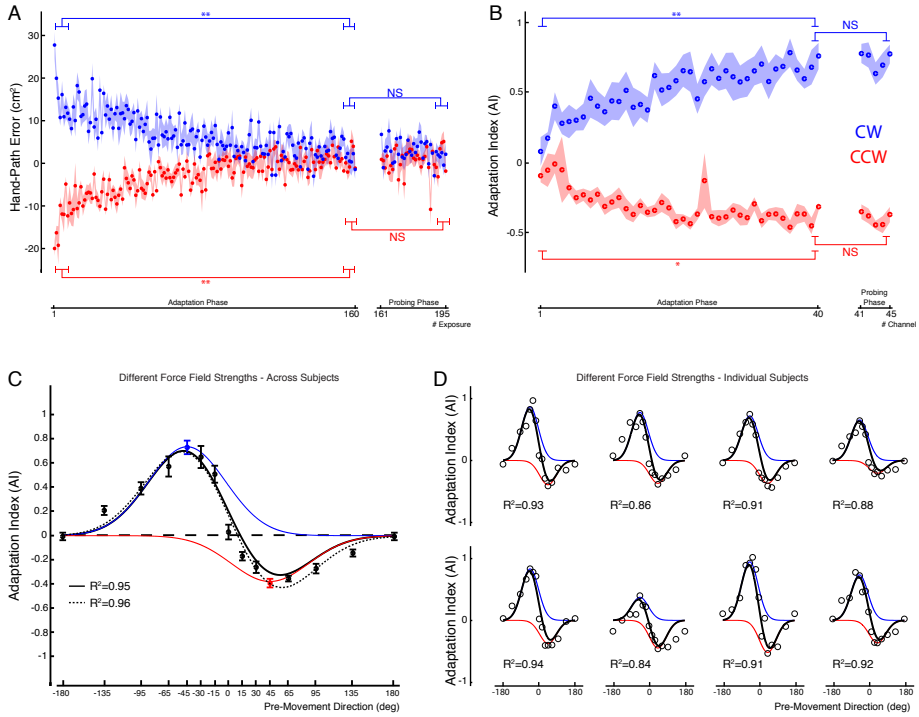


Figure 3.4: Adaptation with unequal strength force fields. *A:* Hand-path error of both force fields during adaptation and probing phase: CW (blue), CCW (red). *B:* Adaptation Index of both force fields during adaptation and probing phase. *C:* Group average data, error bars denote SE. The model predictions are superimposed: black (net expression), single cue representation in red and blue, respectively. *D:* Single subject data with superimposed model predictions.

3.3.6 *Generalization of a single context in the trained hand*

Experiments 1 and 2 involved two pre-movement cues associated with their own force field, CW or CCW. Our model could describe the generalization results assuming two independent, superimposing Gaussians. How valid is this assumption? In a third experiment, using two groups of 8 subjects, we investigated the generalization of a single cue representation (-45° or 45°) after single-force field adaptation.

Figure 3.5A,B show that both groups adapted to the force field, indicated by a significant decrease in hand-path error (both $p < 0.01$) and a significant increase in AI (both $p < 0.001$). A 2-way ANOVA using E (averaged across the final 15 trials of each phase) revealed no significant difference between adaptation and probing blocks ($F_{(1,28)}=0.02$; $p=0.91$), or between the trained pre-movement directions ($F_{(1,28)}=0.13$; $p=0.78$), or interaction ($F_{(1,28)}=1.92$; $p=0.18$). This is also supported by absence of change in AI (taking the mean of the final 2 trials of the adaptation and probing block) for the factor of block ($F_{(1,28)}=2.28$; $p=0.37$), pre-movement direction ($F_{(1,28)}=0.31$; $p=0.68$), and the interaction ($F_{(1,28)}=0.79$; $p=0.38$).

Our main question concerns the generalization around the trained pre-movement cue. As figure 3.5C illustrates the generalization curve is composed of a global (offset B) and a local Gaussian modulation. The overall offset, captured by B, is about 0.4 (SE = 0.02). Furthermore, the local Gaussian modulation had a gain (A) of about 0.46 (SE = 0.02) and a width (σ) of about 27.4° (SE = 1.9°), which is significantly smaller than the width estimated in experiment 1 ($p < 0.001$).

3.3.7 *Pre-movement kinematics cannot explain generalization*

Howard et al. (2012) showed that dwell time, i.e. the time the hand stays in the via-point, influences the expression of an internal model in the subsequent targeted movement. Therefore we checked whether dwell time (the time that the velocity remained below 5cm/s in the via-point) systematically varied with respect to pre-movement direction. We also checked whether peak speed and pre-movement duration (start and

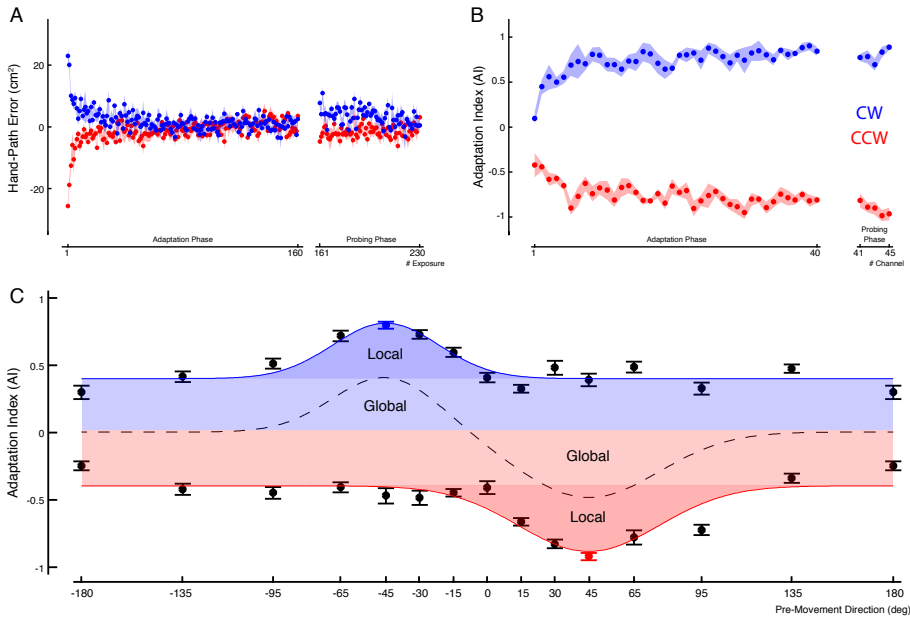


Figure 3.5: Adaptation and generalization to single pre-movement cue representations. *A:* Hand-path error of each group adapting to either a CW (blue) or CCW (red) force field. *B:* Adaptation Index of both force fields (one group each). *C:* Generalization around the trained pre-movement direction. The model fits of single cue representations are superimposed in red and blue, respectively. Group average data, error bars denote SE. Dashed line shows the net sum of the two single cue representations.

	Dwell Time		*Peak Speed*		Duration	
Pre-movement angle	$F_{13,517} = 1.23$	p=0.35	$F_{13,517} = 11.74$	p=0.25	$F_{13,517} = 4.83$	p=0.06
Hand	$F_{1,517} = 0.09$	p=0.81	$F_{1,517} = 0.001$	p=0.97	$F_{1,517} = 0.38$	p=0.63
Trained Hand	$F_{1,517} < 0.001$	p=0.99	$F_{1,517} < 0.001$	p=0.99	$F_{1,517} = 0.04$	p=0.88
Pre-movement angle × Hand	$F_{13,517} = 1.83$	p=0.04	$F_{13,517} = 0.96$	p=0.49	$F_{13,517} = 1.7$	p=0.06
Pre-movement angle × Trained Hand	$F_{13,517} = 10.52$	p<0.001	$F_{13,517} = 0.31$	p=0.99	$F_{13,517} = 0.28$	p=0.99
Hand × Trained Hand	$F_{1,517} = 10.95$	p=0.001	$F_{1,517} = 11.89$	p<0.001	$F_{1,517} = 7.32$	p=0.007

Table 3.1: ANOVA results of the pre-movement analysis. The pre-movement was analyzed with respect to dwell time, peak speed and duration. None of these main factors showed a significant effects and can therefore not explain our results.

endpoint of the pre-movement were determined based a 5cm/s speed threshold) systematically varied with pre-movement direction. We performed 3 ANOVAs, one for each dependent variable (dwell time, peak speed of pre-movement, pre-movement duration) with the factors pre-movement angle, hand and trained hand. None of the main factors was significant and can therefore not explain our results (table 3.1).

With respect to the interactions, the only consistent significant effect across these three dependent variables is the Hand × Trained Hand interaction. In other words, the right hand performed faster reaches when it was the hand that had learned the force fields (trained hand). If the left hand was trained, it performed the faster reaches. This all stems from the far greater number of pre-movements made with the trained compared to the non-trained hand (80% vs 20%).

3.4 DISCUSSION

We studied the generalization of contextual pre-movement cues that enable simultaneous learning of two opposite force environments. Our results show that the force expression based on individual contextual cues follow a Gaussian like pattern around the trained cue. For equal strength force fields this results in a steep fall-off for cue angles between the two trained cues. For unequal force field strengths this also results in skewing the pattern of generalization toward the strongest field. We further

find that these cue related force expression transfer both from dominant to non-dominant hand and vice-versa, in an extrinsic frame of reference. Finally, we show that the generalization of the two simultaneously learnt cue representations cannot simply be described as the combined generalization of single cue representations after adaptation to a single force field.

3.4.1 *Generalization of contextual cues*

Our results confirm previous findings (Howard et al., 2012) that pre-movement cues enable the acquisition of multiple motor memories at the same time. The two cues that were used to provide context for two opposite force fields are single instances from a continuum of possible pre-movement directions, here across angular space. The novelty of our research is that we tested whether and how these single cue instances generalize along the pre-movement dimension.

We show that the amount of force expression reduces with angular separation from the originally coupled cue. We quantified the spatial extent of this generalization by fitting two Gaussian shaped functions to the AIs. The estimated widths of the generalization functions show that the non-dominant hand has a wider cue representation compared to the dominant hand.

Supporting evidence for a wider generalization pattern in the non-dominant hand is also provided by a recent study that used bimanual movements: reaches of one arm were perturbed and uniquely coupled to one movement direction of the other arm (Yokoi et al., 2014). After training, generalization was assessed by measuring force expression of the perturbed arm using error clamps, for different movement direction of the unperturbed arm. Their results also revealed a Gaussian like pattern of generalization, which was wider when the dominant hand was perturbed compared to the non-dominant hand. The authors attribute this finding to the perturbed hand, arguing that the dominant hand shows wider generalization than the non-dominant hand. However, we favor an alternative interpretation. The untrained hand's movement di-

rection served as a contextual cue, implying that the wider generalization is attributed to the non-dominant rather than the dominant hand. What could account for this difference in representation between the two hands?

One explanation is related to the encoding of the contextual cue information. Contextual information derived from the pre-movement can be derived from visual or proprioceptive signals. Visual input is equivalent for both hands and can therefore not explain the difference in width. However, proprioceptive signals are likely to differ: it has been shown that the proprioceptive sense of the non-dominant is more variable than the dominant hand in the central workspace (Wong et al., 2014). As a result, the non-dominant hand's cue information is more variable, which in turn explains a wider generalization pattern.

In our first two experiments we estimated the generalization of individual pre-movement cues based on a Gaussian model fit to the net generalization pattern. In our third experiment we specifically tested the generalization of single pre-movement cue after single force field adaptation. This revealed a global and a local generalization component, which were both different from generalization pattern in the first two experiments, which showed no global component and wider local tuning. We showed that the sum of the independently assessed curves (figure 3.5C, dotted line) does not capture the net generalization curve obtained in experiment 1. What can explain this discrepancy?

A possible explanation may be found in the actual role of a contextual cue. A contextual cue contains information that can successfully aid in distinguishing one force environment from another. If there is only one such environment, then a cue may be superfluous to the information provided by the targeted movement through the force field. If the brain considers the cue irrelevant, subjects will always show full expression of their internal model in the targeted movement, irrespective of the pre-movement direction. However, if the cue is part of the internal model, one could expect a Gaussian fall-off as the direction of the cue-movement changes.

Our data show a mixture of both: the presence of a global component and the narrower tuning of the local component indicate the qual-

itative difference between the information represented by a single pre-movement cue compared to the information represented if two pre-movement cues to two opposite force fields are trained.

An alternative explanation may be that the number of pre-movement cues changes their underlying representation. Support for this notion stems from findings by Thoroughman and Taylor (2005), testing adaptation of reaching movements to perturbing forces that changed directions at different rates relative to the direction of movement. They reported that subjects narrowed the spatial extent of generalization with increasing complexity of the environmental dynamics. In the present case, the increase in complexity is not related to the force fields perturbations but originates in the number of cue related force fields learnt. This could explain why generalization is wider for the single cue compared to the more complex, dual cue experiment. Further support comes from a recent study in which the single cue was not an active but a passively-induced pre-movement (Howard and Franklin, 2015). The authors observed a global AI of 0.6, which is higher than the present AI of 0.4. This larger extent of generalization suggests that the complexity of the environment is lower with passive compared to active pre-movements.

3.4.2 *Transfer of cue-related internal models*

We also show that contextual pre-movement cues transfer to the untrained hand in an extrinsic reference frame, consistent with findings of (Criscimagna-Hemminger et al., 2003; Joiner et al., 2013). This suggests that the internal model and its associated contextual cues share similar underlying representations, although we do not want to claim that a single reference frame is involved. Indeed, recent work has demonstrated that generalization takes place in a mixture of many reference frames (Berniker et al., 2014). In this light, our paradigm only unveiled the net result of multiple underlying reference frames, which appeared to be the extrinsic reference frame.

The present results also speak to the debate about the direction of transfer. Some studies have suggested that internal models are trans-

ferred from the dominant to the non-dominant hand, but not vice versa (Sainburg, 2002; Criscimagna-Hemminger et al., 2003). Our results clearly show transfer in both directions, using a similar adaptation task. What could give rise to this discrepancy?

Studies that showed an asymmetry of transfer across hands used the learning rate as an indicator of transfer (Sainburg, 2002; Criscimagna-Hemminger et al., 2003). In these studies, one hand is first exposed to a force field block and subsequently the opposite hand (learning rate paradigm). If transfer of learning between hands occurs, the subsequent opposite hand should be faster in learning compared to naïve, which is what they found for the non-dominant but not for the dominant hand. In our paradigm we assessed transfer by using error-clamp trials, thereby avoiding any exposure of the untrained hand to the force field. Using this way of testing, we found that about 10% of the learned internal model transferred to the untrained hand, irrespective of hand dominance. We suggest that this difference in transfer can be explained by how it is tested.

If one tests transfer based on increased learning rate, there are two possible ways of how transfer could be revealed: First, learning of the opposite hand could start from a reduced initial kinematic error, caused by the 10% compensatory force transferred from the trained hand, but with the learning rate itself untouched. However, 10% compensatory force is small, and could easily go unnoticed if not specifically tested using error clamps as we did here.

Second, initial errors might start from the same level as naïve, but the reduction of these errors, i.e. learning rate, is ramped up. It was recently shown that the history of errors influences the learning rate (Herzfeld et al., 2014). This means that if errors are experienced during testing of transfer, as in a learning rate based transfer paradigm, the learning rate itself can be influenced by previously experienced errors. However, because we used error clamps, our subjects never experienced any errors while testing transfer. This line of reasoning would suggest that, in a learning rate paradigm, past errors from the trained hand are incorporated differently with respect to transfer – i.e. they are incorporated in

dominant hand learning and ignored in non-dominant hand learning. How could this be explained?

One possibility could be that the uncertainty of the observed errors is part of the internal representation of past errors. In force field learning one source of error is detected through proprioception. Proprioception of the dominant hand is known to be more precise than of the non-dominant hand (Wong et al., 2014). As a result, the internal representation of past errors from the dominant hand may be more precise than that of the non-dominant hand. This difference in precision may explain why the internal model of errors of the non-dominant hand has little effect on the learning rate of the dominant hand. Conversely, the non-dominant hand benefits from the more precise internal representation of past errors of the dominant hand, increasing the learning rate of the non-dominant hand.

Alternatively the difference in learning rate paradigms can also be explained by the suggestion that dominant and non-dominant hand respond different to errors (Shabbott and Sainburg, 2008). This could explain why learning rate studies only reported unidirectional transfer, while our study based on error clamps shows a clear bi-directional transfer between hands.

3.4.3 *Learning rate differences between the dominant and non-dominant hand*

We show that the dominant hand is faster in learning cue-based internal models compared to the non-dominant hand - most prominently seen in error-clamp trials. One might argue that this difference in learning rate is caused by differences in the specialization of the dominant and non-dominant hand. The non-dominant hand may rely more on impedance control and therefore shows less force in the channels, whereas the dominant hand may rely more on feed forward force control (Sainburg, 2002). Alternatively, the learning rate differences could be related to the wider generalization in the non-dominant hand compared to the dominant hand. Internal models with broader generalization curves show more interference, which would slow down learning. This explanation is in

line with Yokoi et al. (2014)'s finding of a slower learning rate when the non-dominant hand codes for context, while the dominant hand is exposed to multiple force fields.

3.4.4 *Implications for models of sensorimotor learning*

Several computational models of motor adaptation have been proposed in the past. However, very few models contain a notion of context that would enable learning of multiple internal models.

The Modular Selection and Identification for Control (MOSAIC) model, proposed by Haruno et al. (2001), entails two parts within its architecture; one part enables internal model selection prior to movement onset and the other permits dynamic selection during movement execution. Lee and Schweighofer (2009) proposed a two-state model containing a fast process (fast learning, fast forgetting) and a slow process (slow learning, slow forgetting) arranged in a parallel architecture to update the beliefs about the perturbations. Their model uses contextual cues to switch between the states associated with the slow process. Thus, in both models, contextual cues serve as discrete switches to select one of multiple internal models.

Only the modular decomposition model proposed by Ghahramani and Wolpert (1997) contains a notion of cue-generalization, but lacks a notion of the learning process. In their study, two unique start positions were coupled to opposite visuomotor mappings. After training, generalization was tested at untrained starting locations. The authors showed that a mixture of Gaussian representations around the trained starting locations could explain the observed pattern of generalization. The present results suggest that their conclusions also apply to force field learning, even with cues that are not part of the perturbed movement itself. In addition, the findings of our second experiment, with unequal force field strengths, show that the mixture proportion of the two internal models is preserved along the pre-movement dimension (i.e. the generalization width remains the same), but that the difference in peak force of the internal models results in a behavioral shift of the generalization curve.

In conclusion, we show that two cue-related internal models are weighted along the cue dimension, modulating a single internal model's contribution to the net motor output. In addition, we show that the untrained hand has access to this representation of internal models and cues in an extrinsic reference frame.

3

4

MASKING AND UNMASKING OF HUMAN MOTOR MEMORIES

Adapted from:
Sarwary AME; Stegeman DF; Medendorp WP; Selen LPJ (2015). *Masking and unmasking of human motor memories*, under revision

4.1 RESULTS

Skilled motor behavior requires the formation of multiple motor memories that can easily be switched and accessed. In tennis for example, one can easily switch from practicing the forehand swing to the backhand swing, without the two memories affecting each other. The forehand training can be continued later and be picked up at a similar level where left off.

Formation of multiple motor memories has been extensively investigated in adaptation of reaching to force field perturbations (Brashers-Krug et al., 1996; Caithness et al., 2004). A recurring finding is that after the acquisition of two motor memories of opposite environmental dynamics in close succession (A then B), re-exposure to the first dynamics (A) does not result in faster re-learning. This has mainly been interpreted in terms of the first memory (A) being erased by the second memory (B) (figure 4.1A, erasure) (Brashers-Krug et al., 1996; Caithness et al., 2004). However, an alternative explanation is that both memories were acquired without affecting each other, but that the original memory A cannot be retrieved on re-exposure because it is masked by B (figure 4.1A, masking). According to this account, the memory of A is not re-learned during the second exposure, but the mask is gradually lifted by shifting the expression of memory B to that of A. How can we distinguish between these two hypotheses when both predict no faster re-learning of the first memory on second exposure?

To dissociate between the erasure and masking hypothesis, we exploit the spatial generalization of motor memories. Previous studies on force field learning have shown that a motor memory acquired for a particular movement direction generalizes toward neighboring movement directions, but this generalization diminishes as the distance from the trained direction increases (figure 4.1C) (Izawa et al., 2012; Donchin et al., 2003; Maschke et al., 2004; Gandolfo et al., 1996). Importantly, these spatial generalization patterns have distinct asymmetric shapes for two naively learned opposite force fields (A and B), providing a unique signature of each motor memory (figure 4.1C).

The erasure and masking hypotheses make different predictions for the shapes of the generalization patterns after having learned two opposite force fields (A and B). If A is learnt first, and its memory (A_{1st}) is completely erased by the subsequent learning of B (B_{2nd}), the generalization curve of B_{2nd} should not be influenced by A_{1st} and should look the same as when probed after being learned naively (B_{1st}) (figure 4.1C). In contrast, the masking hypothesis predicts that the generalization curve of B_{1st} and B_{2nd} will be markedly different, because the generalization curve of B_{2nd} will contain remnants of A_{1st}. These remnants are manifested at spatial target directions where A_{1st} shows stronger generalization than B_{2nd} (figure 4.1C, white space). The same reasoning holds for the opposite force field: i.e. comparing A_{1st} with A_{2nd}, for which A_{2nd} should contain remnants of B_{1st} (figure 4.1D) under the masking hypothesis. We tested these predictions in two experiments: In the first experiment both force fields were trained at the same training direction, whereas in the second experiment the training directions were separated. This results in different amounts of spatial overlap of the respective generalization curves.

4.1.1 *Peeping at the masked memory*

In the first experiment, 16 (15 female) right-handed subjects participated after giving their written consent. Subjects were randomly assigned to two groups (each n = 8) with the opposite order of force field learning ($A_{1st}B_{2nd}$ and $B_{1st}A_{2nd}$, respectively). Subjects had to perform 10 cm center-out reaching movements, while holding the handle of a vBot robotic manipulandum (Howard et al., 2009). After a familiarization phase, the robot imposed a velocity dependent curl force field to the hand, perturbing the reaches directed to the -30° target for 100 trials (figure 4.1B). Field A imposed a clockwise force field; field B delivered a counterclockwise force field. Performance changes during these exposure trials were tracked using the signed Hand-Path error (E) (Franklin et al., 2003). This kinematic error measure computes the integral of perpendicular displacement w.r.t. a straight line, weighted by the forward

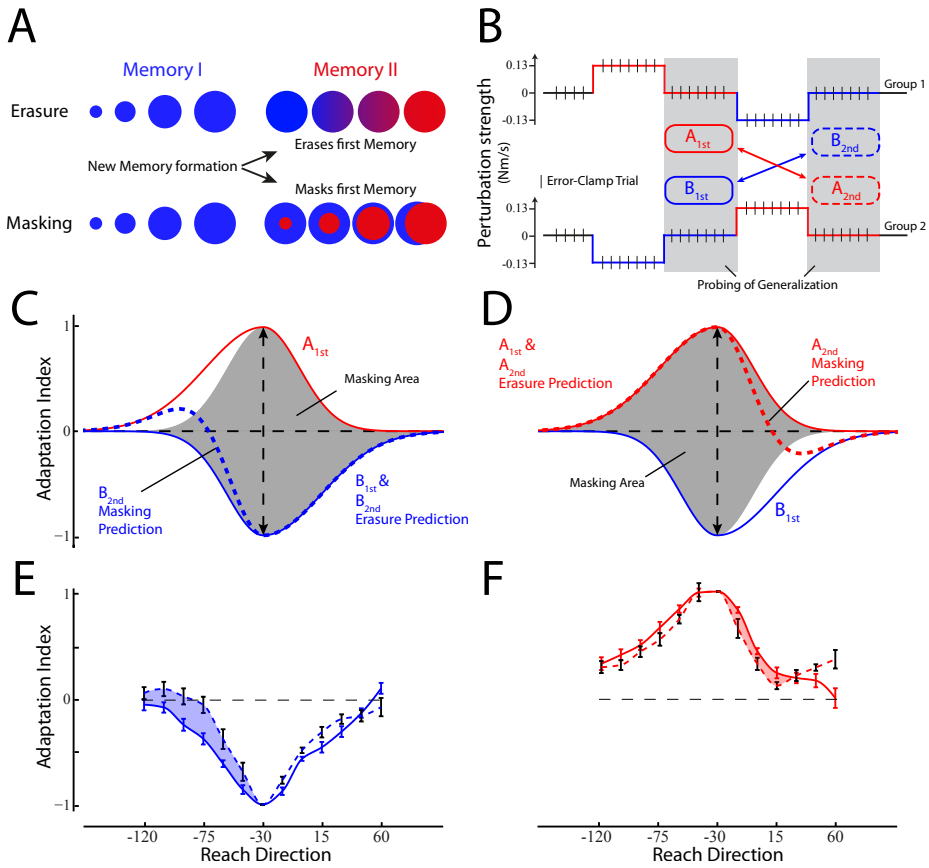


Figure 4.1: *A:* Illustration of the erasure and masking hypothesis when learning two memories. Erasure refers to replacement of the first memory (blue) by the second (red), whereas masking refers to a shift in the expression from first to the second memory. *B:* Schematic of the experiment. After a baseline period, subjects were trained on the first force field for a single target direction. Subsequently they were probed for spatial generalization to non-trained target directions using error-clamp trials. Next they were trained on the opposite force field and again probed for spatial generalization. The two groups had opposite order of the force field directions. *C, D:* Prediction of the spatial generalization patterns for the erasure (solid line) and masking (dashed line) hypothesis for the 2nd learned force field, based on asymmetric naïve generalization patterns (solid line) for the two groups. Force fields were trained for the -30° reach direction. Grey areas denote overlap of generalization patterns relative to the order of learned force fields. *E, F:* Observed spatial generalization patterns as a function of reach direction. Solid lines denote naïve generalization curves: B_{1st} and A_{1st}. Dashed lines represent the non-naïve generalization curves: B_{2nd} and A_{2nd}. Error bars denote SE and the shaded regions indicate significant difference between first and second field learning. Force fields were trained at the same reach direction.

velocity. Motor memories of the curl force field were formed as indicated by a significant decrease in Hand-Path error (paired t-test; average of first 5 versus average of last 5 *E*, each group $p<0.01$, Supplemental Material figure 4.3A, B).

After this first exposure phase, the generalization of the acquired motor memory (A_{1st} or B_{1st}) around the trained target direction was probed every second trial using an error-clamp (13 probe directions, between -120° and 60° in steps of 15°, each repeated 5 times) (figure 4.1B). The other trials were re-exposure trials to the trained force field in order to assure that the expression of the motor memory remained at an asymptotic level. Error-clamp trials, which constrain the reach onto a straight line between the start location and center of the target, allow measurement of memory expression in terms of force production without inducing learning. The force exerted into the error-clamp is regressed against the hypothetical perturbing forces for that trial to obtain an adaptation index (AI), which provides an estimate of the dynamics expected by the subject (Scheidt et al., 2000; Smith et al., 2006). For visualization, the adaptation index was signed by the direction of the force field.

Figure 4.1E and F (solid lines) demonstrate the generalization curves of B_{1st} and A_{1st}, averaged across subjects, showing fall-off of the AI around the trained target direction (-30°). Based on these naïve generalization curves, we can make predictions for the masking and erasure hypothesis when the same fields have to be learned for a second time, i.e. after the opposite field was learnt. The erasure hypothesis predicts no observable difference in generalization between first and second learning (figure 4.1C & D), while the masking hypothesis would be characterized by traces of the first memory in the spatial generalization of the second memory (figure 4.1C & D). More specifically, because the generalization curve of A_{1st} shows less fall-off than B_{1st} for the most leftward reach directions, this part cannot be fully masked by the learning of B_{2nd} (figure 4.1C – white area). Since the compensatory strategies of A and B operate in opposite directions, this results in a steeper fall-off of the generalization curve of B_{2nd} for the most leftward reach directions. Likewise, because the generalization curve of B_{1st} shows less fall-off than A_{1st} for the most rightward reach directions, this part cannot be fully masked by

the learning of A_{2nd} (figure 4.1D). The second phase of the experiment tested these predictions. Subjects had to adapt to the opposite force field over the course of 100 exposure trials (A_{2nd} or B_{2nd}) (figure 4.1B). After learning (see Supplemental Material for learning curves), the spatial generalization was probed as above.

The generalization curve of B_{2nd} is clearly not identical to B_{1st} (figure 4.1E, 2-way ANOVA: Direction, $F_{(12,182)}=65.65$, $p<0.001$; Order, $F_{(1,182)}=44.42$, $p<0.001$), showing a steeper fall-off towards leftward reach directions. Fall-off towards positive directions is not different. Both observations are consistent with the masking hypothesis, which predicted traces of A_{1st} at leftward but not rightward target directions similarly. The generalization curve after the learning of A_{2nd} further supports this notion. Here, as predicted by the masking hypothesis, the generalization curves of A_{2nd} differs from A_{1st} at rightward reach directions, but not at leftward reach directions (figure 4.1F, 2-way ANOVA: Direction, $F_{(12,182)}=59.89$, $p<0.001$; Order, $F_{(1,182)}=10.7$, $p<0.001$).

4.1.2 *Shifting the mask unveils the memory*

Results of experiment 1 are in support of the masking hypothesis. To further validate this claim, we performed a second experiment in which two new subject groups (n=8 in each) again successively learnt two motor memories, but now each associated with a different target direction (A at -30° and B at +15°). By using this difference in target direction, we expect to manipulate the overlap (i.e. the masking area) of the two memories and therefore show how much the spatial generalization of the second memory will mask that of the first (figure 4.2A, B). Under the erasure hypothesis, however, full replacement of the first memory is expected, regardless of the level of overlap.

Results show that both force fields were learned, indicated by a significant decrease in Hand-Path error (paired t-test; average first 5 versus average last 5 *E*, each group $p<0.05$; see Supplemental Material figure 4.3C,D). Figure 4.2C and D show that the spatial generalization curves of the force fields' are clearly different between learned

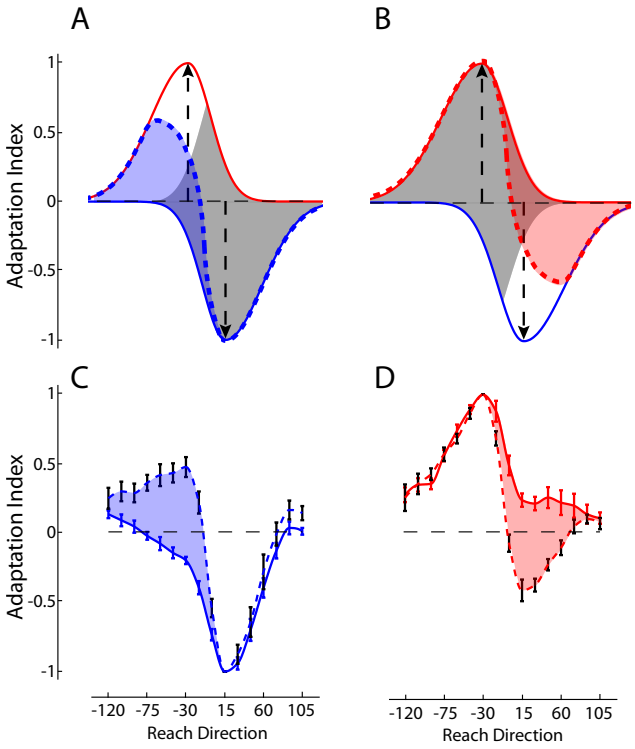


Figure 4.2: *A, B:* Prediction of the spatial generalization pattern based on erasure (solid lines) and masking (dashed lines) hypothesis for different force fields trained in different reach directions (-30° and +15° respectively). *C, D:* Observed spatial generalization pattern as a function of reach direction when the training angle for the two (opposite) force fields is 45° apart. Error bars denote SE. Solid lines denote naïve generalization curves: B_{1st} and A_{1st}. Dashed lines represent the non-naïve generalization curves: B_{2nd} and A_{2nd}. Counterclockwise force field was trained at 15° reach direction. Clockwise force field was trained at -30° reach direction.

first and learning second (B_{1st} compared to B_{2nd}: 2-way ANOVA: Direction, $F_{(15,224)}=91.31$, $p<0.001$; Order, $F_{(1,224)}=135.51$, $p<0.001$; A_{1st} compared to A_{2nd}: 2-way ANOVA: Direction, $F_{(15,224)}=77.68$, $p<0.001$; Order, $F_{(1,224)}=92.22$, $p<0.001$). There is a significantly steeper fall-off toward leftward directions for memory B (figure 4.2C) and towards rightward directions for memory A (figure 4.2D). At zones for which there is no overlap between the spatial memories the generalization mimics the pattern as found for naïve learning.

Taken together, the results of both experiments can be explained by a masking, not by an erasure mechanism.

4.2 DISCUSSION

Our experiments demonstrate that a previously learnt motor memory is masked, not erased, when learning an additional new memory in close succession. While decades of, non-motor, memory research has shown that new memories do not overwrite old memories, but are stored alongside each other, studies in the motor system were not able to confirm this notion because their paradigms could not dissociate between the masking and erasure hypothesis. The current findings resolve this issue based on the spatial generalization characteristics of the memories. We show clear traces of the first memory in the spatial generalization of the second memory, which is in strong support of a masking mechanism. Our findings thus support a general storage and retrieval mechanism that operates similarly for different memory systems. This explains why sometimes older memories are suddenly re-expressed, as observed in paradigms of reinstatement, renewal, spontaneous recovery and reacquisition (Bouton, 2004).

In the motor learning literature, reacquisition paradigms have mainly been used to investigate if previously acquired memories still exist (savings). In these paradigms, opposite force fields are learned in close succession after which subjects are re-exposed to the first learned perturbation. Surprisingly, the reacquisition of this memory is no faster than acquiring it for the first time (Brashers-Krug et al., 1996; Caithness et al.,

2004). However our observation that the two motor memories are stored alongside each other suggests that this lack of faster re-learning is caused by expression of the wrong memory (false memory retrieval).

Our results are consistent with the view that memory formation and memory retrieval are two independent processes (Hunsaker and Kesner, 2013). For memory retrieval a selection mechanism is needed. This selection mechanism needs to classify, based on sensory information and prior experience, the current environment and select the appropriate motor memory. We suggest that this classification process continues to improve even after the memory itself has already been established. This may explain why extensive practice results in fast disambiguation of opposing motor memories (Krakauer et al., 2005) and why in some cases spontaneous recovery is observed (Pekny et al., 2011). Similarly, this classification process is accelerated if sensorimotor cues are connected to the individual memories (Sarwary et al., 2013; Howard et al., 2012). Finally, studies suggest that during a consolidation period the initial memory's neuronal representation is revisited and further processed, thereby improving classification performance. This is reflected in improved performance after a consolidation period (Manoach et al., 2004).

The proposed classification process is consistent with classical ideas of pattern separation and completion in memory research. For pattern separation, incoming information from the two opposite force fields is supposed to be converted by the brain into internal representations (i.e. memories), that can be internally separated despite having very similar inputs. This would occur both during the encoding as well as during the consolidation phase of a memory. On the other hand, pattern completion involves the expression of one specific memory based on limited or noisy sensory information. This process of pattern completion is important for the later retrieval of the correct memory based on limited information (Colgin et al., 2008; Wilson, 2009). Evidence for pattern separation comes primarily from hippocampus studies on episodic memory formation (Bakker et al., 2008; Brock Kirwan et al., 2012; Lacy et al., 2011). However, motor learning seems not so dependent on the hippocampus (Milner, 1962; Milner et al., 1998), suggesting that other neural structures

must be involved that also employ such pattern separation and completion mechanisms.

Motor adaptation studies invariably point to the cerebellum as the crucial structure for learning and adaptation (Ebner et al., 2011; Galea et al., 2011; Miall et al., 2007). The cerebellum is supposed to contain forward models of body and world dynamics that are continuously adapted based on prediction errors. Anatomically, the granule cells that connect via parallel fibers to Purkinje cells and then further to deep cerebellar nuclei are well suited to form an auto-associative network. Indeed, this network organization has been proposed for successful pattern separation and completion (Marr, 1971). Furthermore, resting state imaging studies have shown ongoing increased activity of the cerebellum after adaptation, which may be explained by consolidation through revisiting the memory for pattern separation (Albert et al., 2009).

From a computational perspective, the present and previous findings could be explained by a pattern separation process, which runs simultaneously alongside and beyond the acquisition process. This process is likely part of consolidation itself, within the cerebellum. If pattern separation is poor, switching from expressing one memory (pattern completion) to the other is a gradual process. When the pattern separation process has not fully been completed, the pattern completion process needs more contextual information from the environment, which in adaptation paradigms is acquired over time. This, in turn, results in an apparent lack of savings as observed in previous studies, which could erroneously be interpreted as the older memory being erased.

4.3 SUPPLEMENTAL MATERIAL

4.3.1 *Reach task*

Subjects had to perform 10 cm reaching movements in the mid-sagittal plane, about 30 cm in front of the torso. At the beginning of a trial, the start position (in grey, 1.5 cm radius) and target position (in yellow, 1.5

cm radius) were simultaneously displayed. A red cursor (0.5 cm radius) indicated the hand position.

Before the start of the trial the subject had to place the hand cursor within the start position and stay still (cursor speed < 5cm/s for 100msec). Then, a tone instructed to start the reach. If the reach was initiated before the tone or started >1s after the tone, an error message appeared on the screen ('wait for beep' or 'move after beep') and the trial was repeated. The start of the movement was defined as the first point where the hand speed was > 5cm/s after the tone was given. The endpoint of the movement was defined as the first point where the speed < 5cm/s. If this endpoint was within the target position the target turned from yellow to green. If the endpoint was not within the target position a feedback message was given ('stop at target'). If the endpoint was within the target position, but the movement duration was > 500msec a 'move faster' feedback message was given. These feedback messages were used to make the reaches more consistent, but did not lead to rejection of the trial.

During the target movement the motors could be off (null), produce a curl force field (clockwise or counterclockwise) or produce an error clamp (Scheidt et al., 2000; Smith et al., 2006).

Perturbations were induced using a curl force field. Forces were produced that are perpendicular to movement direction and proportional to the reach velocity:

$$\begin{bmatrix} F_x \\ F_y \end{bmatrix} = b \begin{bmatrix} 0 & -1 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} \tag{4.1}$$

in which the damping constant b was set to ± 13 · Ns/m. The sign of b determined the direction of the force field, where A was a CW and B a CCW force field.

Error-clamp trials constrain the movement onto a straight line from the start to the target position. The hand was constrained to a straight line using a spring constant of 6,000 N/m. Both the curl force fields and error clamps were initiated at the onset of the tone that signaled the start of the reach. Damping and spring constants were linearly ramped

up over 50 msec. During adaptation a batch of 10 trials contained one error-clamp trial. These were included to measure the development of the motor memory.

During the probing phase of the generalization curve, subjects made reaches to 13 targets (experiment 1: -120 to 60 degrees in steps of 15) while being error-clamped. Every second trial was a re-exposure trial to the trained force field at the trained target direction. This was done to assure that force expression remains at an asymptotic level. In experiment 2, the probing phase of the generalization curve consisted of 16 target directions (-120 to 105 degrees in steps of 15). Again every second trial was a re-exposure trial to the force field at the trained target direction.

4.3.2 *Analysis of learning*

Learning over trials was assessed by computing the signed hand-path error measure (E):

$$E = \int_{t_0}^{t_f} x(t) \cdot \dot{y}(t) dt \tag{4.2}$$

where x(t) is the perpendicular distance of the actual trajectory compared to a straight line joining start position and target position and $\dot{y}$(t) is the hand velocity in the direction of the target (Franklin et al., 2003).

Learning was also assessed looking at the adaptation index (AI, see main text for description) over the course of training during each adaptation block. Figure 4.3 shows the hand-path error (E) and the AI over trials of experiment 1 and 2 in all adaptation and probing blocks. Both the significant decrease of E ($p<0.05$) and the significant increase in AI between the first and last trial in the adaptation block ($p < 0.05$) indicate that subjects learned to deal with the curl-field dynamics.

4.3.2.1 *Analysis of generalization*

To determine differences between generalization curves, we used 2-way ANOVAs on the results from each force field and each experiment. Each

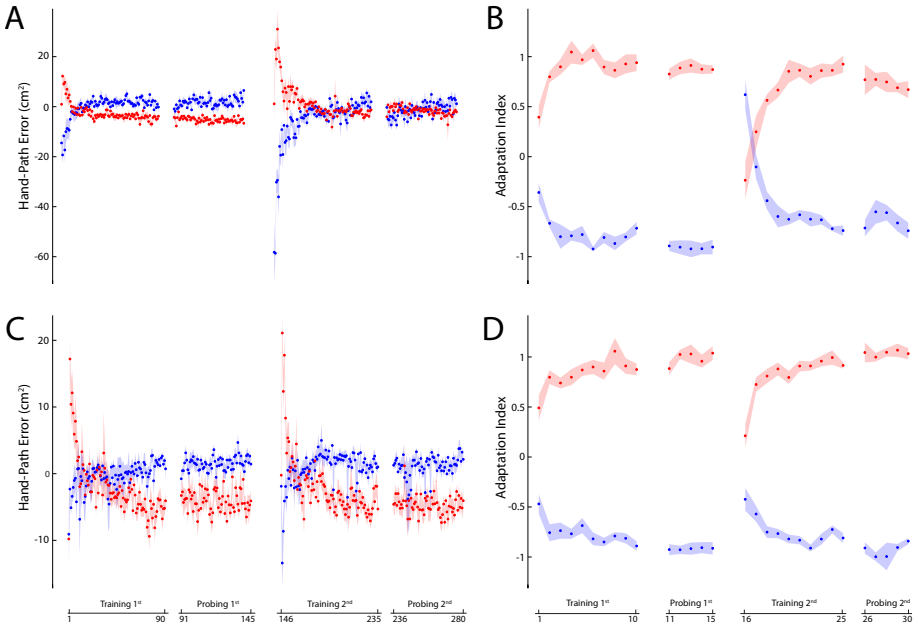


Figure 4.3: Hand-path error *E* (left panels) and Adaptation Index (right panels) during adaptation and probing phases of both experiments, averaged across subjects. Shaded areas denote SE. Top row, experiment 1, training both force fields at -30°; bottom row, experiment 2, training CCW force field at -30° and CW force field at 15°. Red refers to CW and blue to a CCW force field.

ANOVA had two factors: *Direction* and *Order*. In experiment 1, the factor *direction* contained 13 levels: the values ranged from -120 to 60 degrees in steps of 15 degree. In experiment 2, this factor had 16 levels and direction values were ranging from -120 to 105 degrees in steps of 15 degree. The other factor *order* had two levels, 1st and 2nd, indicating at which stage the generalization curve was assessed.

5

FLEXIBLE TUNING AND UPDATING OF MOTOR PRIMITIVES TO REDUCE MOTOR INTERFERENCE

Adapted from:
Sarwary AME; Stegeman DF; Medendorp WP; Selen LPJ (2015). *Flexible tuning and updating of motor primitives to reduce motor interference*, in preparation

5.1 INTRODUCTION

We constantly adapt our movements in response to dynamic changes of our body and the environment. This adaptation process results in adjustments of the internal representation of the dynamics of body and environment. These adaptive changes of the internal model are not restricted to the trained condition, but also generalize to similar conditions. For example, when adapting reach behavior to a new force environment, a Gaussian shaped generalization curve will be observed around the trained target direction (Maschke et al., 2004; Izawa et al., 2012). These generalization patterns provide a window into the underlying neuronal encoding of the internal model (Thoroughman and Shadmehr, 2000; Donchin et al., 2003; Poggio and Bizzi, 2004).

This encoding of the internal model has often been modeled as a network of basis functions, i.e. motor primitives, which are specified as Gaussian-like tuning functions, evenly distributed across space. Adaptation in the network is achieved by updating the primitives' weights, with ongoing debate whether the update should be credited to the planned motion, i.e. plan-referenced learning (Pouget and Snyder, 2000; Poggio and Bizzi, 2004; Thoroughman and Taylor, 2005), or the actual motion, referred to as motion-referenced learning (Gonzalez Castro et al., 2011). The latter offers a safer updating mechanism with respect to stability.

However, adaptation in a motor primitives network may not only be governed by weight changes, but also by modulation of the tuning widths of the motor primitives, depending on the complexity of the external environment (Thoroughman and Taylor, 2005). Thoroughman and Taylor (2005) tested adaptation in a viscous force field, increasing task complexity by changing the direction of the perturbing force at higher rates than the direction of movement. Subjects were able to learn force fields of any complexity but the extent of generalization narrowed with increasing complexity.

It can be argued that task complexity also changes when two opposite force fields interfere while adapting two them. In this case, task complexity relates to the level of interference, which can be increased by

reducing the angular separation between the targets at which the two fields are learnt.

We hypothesize that in this case the tuning of motor primitives will also sharpen to reduce interference between the representations of the two force fields as target separation decreases. This sharpening of primitives would be most beneficial if adaptation were to occur based on plan-referenced learning for close targets. In this case, plan-referenced learning would maximize the distance between the neuronal representations of the two internal models. In contrast, if adaptation were to occur based on motion-referenced learning, sharper tuning would not provide an advantage because the actual performed reaches associated with the two perturbations would cover the same workspace and weight updates would still interfere. Given the different advantages of updating mechanism under low and high interference levels, we further hypothesize that the weight updating mechanism will gradually shift the credit assignment from motion to plan-referenced learning as a function of target separation.

We tested these hypotheses by asking subjects to make center-out reaching movements **(**Fig. **5.1)**, while adapting to two opposite force fields simultaneously. Different groups were exposed to the same opposite force fields, but with different degrees of angular separation between the targets associated with the fields. Perturbations of the force fields were directed towards the opposite field's target so that movement error distributions for the two force fields start to overlap when the target separation decreases. After adaptation, we tested generalization at untrained targets.

We first show that the rate of learning two force fields reduces depending on their degree of separation and is directly linked to the extent of generalization. Next we show that the underlying encoding and weight updating process changes depending on induced interference levels. The closer the force fields, the narrower the motor primitives' tuning becomes and the more updating occurs by crediting plan-referenced learning.

5.2 MATERIALS AND METHODS

5.2.1 *Participants*

All experiments were conducted under the general approval for behavioral experiments by the institutional ethics committee of the social science faculty of the Radboud University Nijmegen. Subjects gave their written consent to participate in the experiments and were financially reimbursed. All 40 subjects (29 female; mean = 22.8, SD = 3.5) were naïve to the task and had normal, or corrected to normal vision and had no known motor deficits. Each subject was right-hand dominant and had a laterality index of 100 according to the Edinburgh test of handedness (Oldfield, 1971).

5.2.2 *Apparatus and setup*

Subjects sat on a height adjustable chair in front of a robotic rig (Fig. 5.1A**)**. Their right arm rested on an air sled, which was floating on a glass top table. Reaching movements were performed in the horizontal plane, while holding the handle of a planar robotic manipulandum, vBot (Howard et al., 2009). Robot positions and force output were updated at 1000 Hz. Stimuli were presented in the plane of movement using a semi-silvered mirror, reflecting the display of a LCD monitor suspended horizontally above (Fig. 5.1A**)**. This setup allowed veridical feedback of the hand position (a red circle of 0.5 cm radius), while at the same time preventing view of the arm. The start and target position of reaching movements were indicated by grey and yellow circles of 1.5 cm radius, respectively.

5.2.3 *Reach task*

Subjects performed 10 cm reaching movements. At the start of a trial both the start and target position were displayed. Subjects had to place the hand cursor in the start position and stay still (hand speed < 5cm/s)

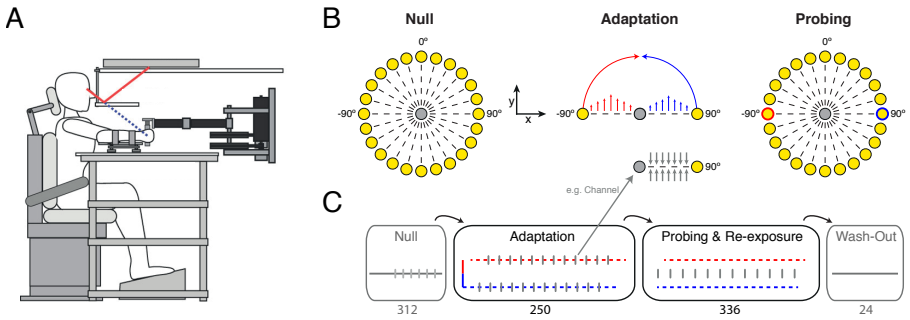


Figure 5.1: Experimental design. **A.** Setup: Subjects were seated in front of a robotic rig performing reaches holding the handle of a planar robotic manipulandum (vBot). The arm performing the task was resting on an air sled floating on a glass top table. Courtesy of Franklin and Wolpert (2008). **B.** Task: Reaches were performed starting in the center to one of 24 targets. 3 Panels illustrate the targets during null, adaptation, and probing block. The adaptation and probing block illustrate the group with 180° target separation. Red denotes CW, blue denotes CCW force field. **C.** Paradigm: Illustration of the force field schedule within an experimental session. Grey bars denote error clamp trials.

for 200 ms. After this period a tone indicated the start of the reach. The trial was repeated if the reach was initiated before the tone or later than 1s after the tone. In both cases an error message appeared on the screen ('wait for beep' or 'move after beep'). The start of the reach was defined as the first point to when the hand speed exceeded 5 cm/s, whereas the end of a reach was defined as the first point for which hand speed was below 5 cm/s. Subjects had to reach the target within 500 ms. The target position turned green when the hand cursor entered it. Subjects were instructed to stay at the target position for 200 msec. At the end of the trial, additional feedback was provided if the endpoint was not within the target position ('stop at target'), the movement duration was longer than 500 ms ('move faster'), or if the cursor moved through the endpoint ('stay at target'). Feedback messages were used to increase consistency across trials, but did not lead to rejections of trials.

During the trial, the motors of the vBot where either turned off (null), or produced a velocity dependent curl force field (clockwise, counter-clockwise), or generated an error clamp (Scheidt et al., 2000; Smith et al., 2006).

A *velocity dependent curl force field* produces forces perpendicular to the instantaneous movement direction and proportional to the movement velocity, described as follows:

$$\begin{bmatrix} F_x \\ F_y \end{bmatrix} = b \begin{bmatrix} 0 & -1 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} \tag{5.1}$$

were b, the field constant was set to +13 (CW) or -13 (CCW) Ns/m.

An *error clamp* constrains the movement onto a straight line from start position of the reach to target position. To constrain the reach onto a straight path a spring constant of 6,000 N/m was used without additional damping. The curl force fields as well as the error clamps were initiated at the onset of the tone.

At the end of the reach, subjects were instructed to relax their arm, as they were automatically returned to the start position for the next trial. This passive return movement followed a minimum jerk profile with a duration of 700 msec. The hand was pulled onto this trajectory by a PD-controller with a spring constant of 3,000 N/m and a damping constant of 2.5 Ns/m.

5.2.4 *Paradigms*

Five groups of 8 subjects each performed the reach task. Each group made reaching movements to two targets and adapted to the two force fields (CW and CCW), associated with the targets, simultaneously. The separation of the two trained targets differed across groups (180°, 90°, 15°, 5°, 0° separation). In total 24 targets were defined on a 10 cm radius circle around the start position ranging from -180° to 165° in steps of 15° (Fig. 5.1B).

To get accustomed to the experimental conditions and passive robot dynamics, subjects started each experimental session with 312 null trials

(13 batches of 24 targets) (Fig. 5.1C). Each batch contained the presentation of the 24 targets in random order. Within these 13 batches, baseline force expression into the error clamps was randomly probed 5 times for each possible target.

An adaptation block of 250 trials followed this familiarization block. During this adaptation block, subjects were trained on two force fields simultaneously. The separation of the two trained targets differed between the five groups: 180° (-90°, 90°); 90° (-45°, 45°); 15° (-7.5°, 7.5°); 5° (-2.5°, 2.5°); 0° (0°, 0°). Negative target angles (left of body midline) were always coupled with a CW force field, whereas positive target angles (right of body midline) were always coupled with a CCW force field. The 0° separation group was exposed to both CW and CCW force fields at the 0° target. The two targets, and thus also force fields, were presented pseudo randomly, such that 10 trials contained 4 CW trials, 4 CCW trials, and 2 error clamp trials, one for each target. The error clamp trials measured the level of adaptation across trials.

After the adaptation block, a probing block followed, in which generalization of the force fields to non-trained targets was assessed (Fig. 5.1B, C). Forces into the error clamp were measured for all 24 targets. These error clamp trials were intermixed with re-exposure trials to the two trained targets and force fields (every 2nd trial) to keep adaptation at an asymptotic level throughout the probing block. Every target was probed 7 times. The -15° and 15° targets were replaced in the 15° separation group by -7.5°, 7.5° and in the 5° separation group by -2.5°, 2.5°.

The experimental session ended with a washout block of 24 trials, one reach to each target.

5.2.5 *Analysis*

Data were stored for offline analysis using MATLAB (The MathWorks). Learning and generalization were assessed from error clamp trials, where we computed an adaptation index (AI), which represents the degree of force compensation to the curl force field. The AI was computed by regressing the theoretically produced curl force field based on hand

velocity against the actually produced force in the error clamp. This provides a regression coefficient between -1 and 1 (Smith et al., 2006). The sign was introduced to indicate the direction of compensatory force, positive CW, negative CCW and simplified illustration of generalization to two opposing force fields. AIs were baseline corrected by subtracting the average AI obtained in the familiarization phase of each target.

AIs within the adaptation block were first compared across force fields to determine if learning occurred similarly within groups using an ANOVA. Afterwards AIs were collapsed over CW and CCW after flipping the sign of the CCW force field. Statistical comparisons in the adaptation block were made on the collapsed CW and CCW AIs. To assess if learning occurred in the adaptation block, we compared the average of the first 5 versus the average of the final 5 AIs from this block using a paired t-test. To test if adaptation levels remained constant throughout the probing block, we performed a 2-way ANOVA with the factor Block (adaptation, probing) and group (180°, 90°, 15°, 5°, 0°) using the average of the trials in the probing block and the equivalent number of the last trials in the training block.

5.2.6 *Parameter estimation and simulation*

Generalization is often modeled by a network of motor primitives, each specified by a Gaussian-like tuning function (Krakauer et al., 2000; Thoroughman and Shadmehr, 2000; Donchin et al., 2003; Poggio and Bizzi, 2004; Pouget and Snyder, 2000). Here we use a similar modelling approach to determine underlying changes in encoding and learning mechanism during simultaneous adaptation to opposite force fields with varying degrees of target separation. We therefore estimated the parameters of the motor primitives from the measured generalization and learning curve.

In the model, each primitive g_j is represented by a Gaussian-shaped function (Donchin et al., 2003; Brayanov et al., 2012; Ingram et al., 2013; Yokoi et al., 2014):

$$g_j(\theta) = ae^{-\frac{(\theta-\mu_j)^2}{2\sigma^2}} + b \tag{5.2}$$

in which θ is the reach direction, a is the gain, b represents the offset (defined as $1 - a$), σ defines the width of the Gaussian primitives, and μ is the preferred direction (PD). The total number of primitives was set to 20, which were equally distributed across angular space (-180° to 180°), and together encode an internal model of environmental dynamics. Parameter a was set to 0.97 (Yokoi et al., 2014).

The output of the model, $\hat{f}$, at the i^{th} trial is computed by a linear summation of the activity of the motor primitives for the planned movement direction ($\theta_{planned}$):

$$\hat{f}^{(i)} = [w^{(i)}]^t g(\theta^{(i)}_{planned}), \tag{5.3}$$

here w and g are row vectors representing the primitives' weights and the movement direction dependent activity of each primitive. The updating process of the internal model across trials occurs through changes of the weights w, driven by the prediction error (ε) between the actual force (f) and expected force ($\hat{f}$):

$$\varepsilon^{(i)} = f^{(i)} - \hat{f}^{(i)} \tag{5.4}$$

The updating of the weights can occur relative to plan or motion-referenced learning. Here we combine these two updating schemes of the weights:

$$w^{(i+1)} = \alpha w^{(i)} + \varepsilon^{(i)} K[\gamma g(\theta^{(i)}_{planned}) + (1-\gamma) g(\theta^{(i)}_{actual})] \tag{5.5}$$

The parameters of the weight updating equation are the retention factor α, the learning rate K, and the relative contributions of the two updating schemes, quantified by γ. To calculate θ_{actual} we need to convert the force error (ε) into a kinematic error, for which we assume a simple linear mapping (A):

$$\theta^{(i)}_{actual} = \theta^{(i)}_{planned} + \varepsilon^{(i)} A \tag{5.6}$$

We assumed that α, K, and A are independent of the separation between the two trained targets. However, the contribution of plan and motion referenced learning (i.e. γ) was expected to depend on the separation of the trained targets. In addition, the width of the Gaussian primitives (σ) was also allowed to vary for the different target separations. This results in a model with 11 free parameters (α, K, A, σ_{180}, σ_{90}, σ_{15}, σ_{5}, γ_{180}, γ_{90}, γ_{15}, γ_{5}).

To assess parametric differences for σ and γ across groups, we fitted this model to the learning and generalization data of the groups with 180°, 90°, 15°, 5° separation simultaneously using 1000 bootstraps. The perturbation sequence, provided to the model, was equivalent to the trial structure of the training block subjects received. Parameter comparisons were made using the 95% confidence interval of the bootstrap distribution. The parameters determined for the 5° separation group were used to make a prediction for the 0° separation group.

5.3 RESULTS

Five groups of subjects were trained to adapt to two opposite force fields. The five groups differed in the angular separation of targets that were associated with the opposite force fields (180°, 90°, 15°, 5°, 0°). After learning we probed the extent of spatial generalization at non-trained target directions. Our hypothesis was that the closer the two trained targets are, the lower the learning rate and final adaptation level, both due to increased interference. Furthermore, we hypothesized that to increase discriminability between internal representations, the underlying tuning width will decrease and the update mechanism will shift from motion to plan-referenced learning. To test these ideas, we used a modeling approach in which motor primitives and weights form the representation of the two internal models. This model is supposed to capture learning and generalization and generalization differences at the same time.

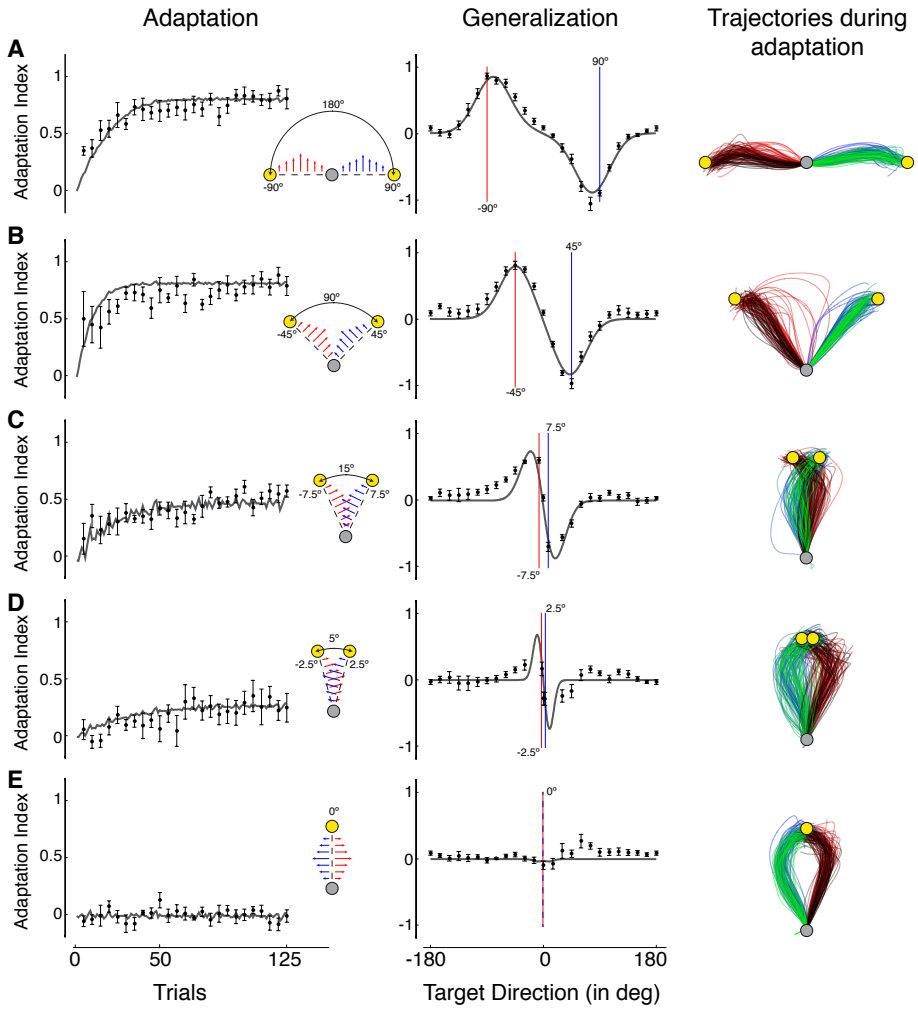


Figure 5.2: Adaptation Index during learning (left panel) and probing phase (middle panel) averaged across subjects. Right panel shows trajectories during adaptation of a representative subject of each group. Evolution across trials is color coded for CW from red to black; CCW blue to green. A-E: Separation group 180° to 0°. Error bars denote SE. Median of the bootstrap fitting procedure is overlaid in grey. The model prediction for the 0° separation group is based on parameters estimated for the 5° separation group.

5.3.1 *Adaptation to two opposite force fields*

First we assessed if learning within each group differed across force fields. To test this, we ran a 2-way ANOVA within each group with the factors epoch (25 levels) and force field (CW or CCW). Each ANOVA revealed no significant differences for the epoch x force field interaction (each $p > 0.05$). We therefore collapsed AIs of CW and CCW force fields, after flipping the sign of the CCW AIs.

All groups, except for the 0° separation group, showed signs of adaptation to the two opposite force fields **(**Fig. 5.2A-E**)**. The 180° separation group showed the strongest final adaptation, signified by a final AI of ~0.8 for the collapsed CW and CCW data **(**Fig. 5.2A**)**. The final level of adaptation comes down systematically if the trained targets come closer **(**Fig. 5.2A-D**)** with zero adaptation if the fields are not dissociated by the target location **(**Fig. 5.2E**)**. Adaptation is confirmed in all groups by a significant increase in AI (average of first 5 versus last 5 trials; each $p < 0.05$), except for the 0° separation group ($p = 0.87$).

After the adaptation block, we assessed the extent of spatial generalization of the acquired internal models in a probing block. During the probing block, it is important that the level of adaptation remains at the same level as at the end of the adaptation block so generalization can be assessed at an asymptotic state. To test this, we ran a 2-way ANOVA with the factors block (training, probing) and group (180°, 90°, 15°, 5°, 0°), comparing AI averaged across the final 7 trials of the training versus probing phase. The ANOVA revealed no significant effect of block ($F_{1,70} = 3.82$; $p = 0.12$) or block x group ($F_{4,70} = 0.66$; $p = 0.62$), which confirms that the level of adaptation remained unchanged during the probing phase. As expected based on figure 5.2A-E, there was a significant effect of group ($F_{4,70} = 145.86$; $p = 0.0001$), because adaptation levels decrease with smaller target separation.

5.3.2 *Generalization of two opposite force fields*

Our data indicate that subjects can learn two opposite force fields simultaneously, but that the amount of learning depends on the target separation. The next question is how the two acquired internal models generalize over the workspace.

Figure 5.2 (middle panel) illustrates AI as a function of the probed target direction. The groups show clear systematic spatial generalization, but not the 0° separation group. However, the pattern is very different for the different trained target separations. First, the peaks and troughs of the generalization curve in the 180° group are not aligned to the trained target locations, but shifted in the direction of the force fields. This can be observed mostly for the 90° target. The shift seems to decrease, and even disappear, when trained target separation decreases. This observation may be the result of a shift from motion-referenced updating to plan–referenced updating during the learning stage of the experiment. Additional evidence for this comes from observing the raw trajectories in figure 5.2 (right panel). The reaches of the 15° and 5° separation group clearly show that the trajectories of each force field cross covering opposite parts of the workspace. If motion-referenced learning were to remain in the 15° and 5° separation group, then the peaks of the generalization curves should have been mirrored along 0°. However, the generalization profiles clearly show that the peaks remain close to the actual targets.

Second, the spatial generalization seems to become narrower as the trained target separation decreases. The question is whether the narrowing of the spatial generalization is due to changes in the motor primitives' width.

To test the above ideas, we modeled both the learning and generalization in a network of motor primitives and weights that form the representation of the two competing internal models. Important ingredients to this model are the variable width (σ) of the motor primitives and the target separation dependent contributions of motion-referenced and plan-referenced updating of the weights (γ). This model, containing 11 free parameters, was fitted to the data from all groups simultaneously

using 1000 bootstraps. Within each group 8 random draws were made for one fitting step.

The median learning curves and generalization patterns from the bootstrap distribution are overlaid onto the data points in figure 5.2 (grey). The model clearly captures the behavioral patterns for the different groups, as evidenced by an R^2 value of 0.92 ($p < 0.0001$). The R^2 confidence interval of the bootstrap distribution goes from 0.89 to 0.94, with all fits being highly significant (all $p < 0.001$).

Differences among groups in learning and generalization are only captured by the model parameters σ_{180}, σ_{90}, σ_{15}, σ_5 and γ_{180}, γ_{90}, γ_{15}, γ_5, because these were only allowed to vary among groups. Figure 5.3A shows that the tuning width of the motor primitives (σ) significantly decreases as the two trained targets' separation decreases. Figure 5.3B shows that for large target separation, updating takes predominantly place relative to motion-referenced learning and that planned-referenced learning takes over as the targets become closer, by a significant increase of γ.

The results of the global parameters are: $\alpha = 0.987[0.982\ 0.991]$; $K = 0.068[0.055\ 0.10]$, and $A = 80.2[79.9\ 81]$.

5.4 DISCUSSION

We studied simultaneous learning and generalization of two opposite internal models, each trained at a specific target direction. Across subject groups we systematically varied the angular separation between these two targets to modulate interference levels. Our modeling results show that the rate of learning of the two internal models reduces as a function of target separation and is directly linked to the extent of generalization. Furthermore, to combat interference between representations, the tuning width of the motor primitives decreases when the angular separation between the targets decreases. In addition, the updating of the internal representation gradually shifts from motion-referenced to plan-referenced learning.

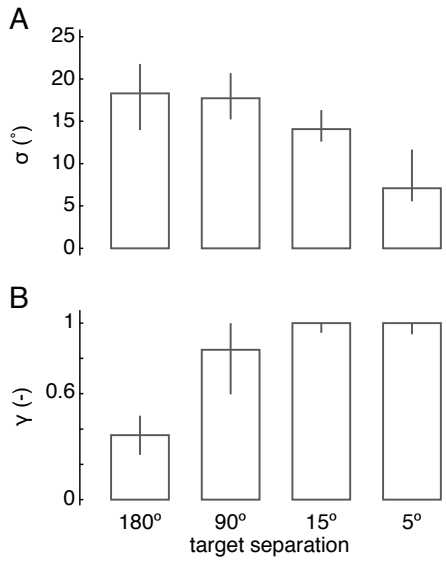


Figure 5.3: Estimated σ and γ parameters across groups. **A.** Estimated σ parameter becomes smaller with reduced target separation. **B.** Estimated γ parameter becomes larger with reduced target separation, indicating more reliance on plan-referenced learning.

5.4.1 *Sharpening of tuning*

Our experimental data show a clear reduction in the spatial extent of generalization when the two targets associated with the two force fields get closer. The fits of our motor primitives model indicate the need of sharpening of the Gaussian shaped primitives to explain this observation. A similar decrease in tuning width has been suggested to occur when task complexity increases (Thoroughman and Taylor, 2005). Task complexity was increased by modifying the rate of change between the direction of the perturbing forces and direction of hand velocity. In contrast to Thoroughman and Taylor (2005), we did not alter task complexity by changing force field parameters. We trained two force fields simultaneously, which were associated with different targets. Next, we induced different interference levels by altering the degree of target separation. Our results

show that under increased levels of interference, tuning widths narrow. Why would this occur?

We suggest that narrowing tuning width results in increased discriminability between targets and their associated internal models, thereby decreasing the interference between the two representations. Support for this comes from our learning data, showing that even with very little target separation, substantial learning occurs. If the tuning widths were to stay fixed at the values observed for the 180° separation, learning would have deteriorated significantly more for the 15° and 5° target separation groups. Further evidence comes from the generalization curves obtained from these two groups. In both groups, clear generalization can be seen for each force field at its respective trained target. But why then is tuning width not invariably narrow to assure high discriminability in any condition? It is important to note that high discriminability goes at the expense of generalization, which assures transfer of learning from one situation to similar ones. This suggest that there is a trade-off between discriminability and the extent of generalization.

Flexibility in neuronal tuning width has also been observed at the neurophysiological level. Neurons in primary motor cortex showed sharper tuning after adaptation to a single force field (Gandolfo et al., 2000) or a single visuomotor rotation (Paz and Vaadia, 2004). Similar changes in tuning width have been observed in macaque MT during a speed discrimination experiment, presumably resulting in higher levels of speed discriminability (Krekelberg et al., 2006). Sharpening of tuning has also been found in V4 during attention tasks (Spitzer et al., 1988; Lee et al., 1999), and in V1 during perceptual learning and adaptation (Schoups et al., 2001; Teich and Qian, 2003).

Although narrowing of neuronal tuning has been explicitly observed experimentally and implicitly derived from behavior, the algorithm driving this adaptation remains elusive. Recent research proposed an extension of the motor primitives updating model to with a mechanism that adjusts neuronal tuning width during learning. In this locally weighted projection regression (LWPR) model, adjustment of weights and tuning width are both driven based on motor error (Marongelli and Thoroughman, 2013). Such an updating mechanism of both the primitives' weights

and tuning widths might be implemented in the cerebellum, which has been identified to play a crucial role in motor learning (Wolpert et al., 1998; Galea et al., 2011). Its neurophysiological structure would support such a mechanism as it does receive error signals via climbing fibers (Kitazawa et al., 1998), possibly adjusting individual purkinje cells contributions and altering broad tuning of purkinje cells (Coltz et al., 1999).

5.4.2 *Shift from motion-referenced to plan-referenced learning*

Classical modeling approaches using motor primitives implemented the updating process relative to the planned target direction, i.e. plan-referenced learning (Thoroughman and Shadmehr, 2000; Donchin et al., 2003; Thoroughman and Taylor, 2005). However, recent research has suggested that the updating process does not occur relative to the planned motion, but relative to the actual motion (motion-referenced learning, (Gonzalez Castro et al., 2011). Motion-referenced learning predicts that, especially during the early stages of learning, the generalization curve peaks in the direction of experienced errors (Gonzalez Castro et al., 2011). Our results for the largest target separation are consistent with this notion. Generalization curves are skewed in the direction of the force field perturbations and also our primitives model puts most weight to the motion-referenced updating part. However, if motion-referenced learning would be the only updating mechanism, our generalization data should have shown a mirrored generalization pattern around 0° for the closer target separation groups. For instance, in the 15° separation group, training of the CW field occurred at -7.5°, whereas the CCW field was trained at 7.5°. However, the actual movements planned towards the -7.5° target covered the 7.5° workspace and vice versa (Fig. 5.2C). If updating had been motion-referenced this should have resulted in the CW field's representation being most prevalent at around 7.5°, and the CCW field's representation at around -7.5°, which is not what we found (Fig. 5.2C). Rather than motion-referenced updating, our results suggest a plan-referenced updating mechanism for closer targets. The advantage of shifting from motion-referenced to plan-referenced learning is again

increased discriminability. In other words, the nervous system actively tries to reduce overlap of representations, to avoid constantly updating the same weights in opposite directions, which results in no learning.

Similar as to neuronal tuning to be flexible, our results suggest that the associated weights to be updated is also flexible and learning does not purely occur relative to plan or motion-referenced learning. We suggest that mechanistically, this shift in learning does not occur based on error itself, but rather based on overlapping error distributions in space **(**Fig. 5.2, right panel**)**. In the case of this study, error distributions in space start to overlap in the 90° target separation group and even cross over relative to 0° in the 15° and 5° groups **(**Fig. 5.2, right panel**)**. Already in the 90° group a significant decrease in pure motion-referenced learning can be observed. But how does the brain infer that error distributions are overlapping?

One possible way for the nervous system to assess overlapping error distributions would be to determine the variance of errors in space. If errors overlap in space, it would result in high variance and weights would constantly be updated in opposite directions. Reducing this variance could be accomplished by a shift from motion to plan-referenced learning in our task.

In conclusion, our data suggest two mechanisms to reduce interference in motor learning: the flexible adjustments of neuronal tuning width and a flexible weighting between motion-referenced and plan-referenced learning.

5

Part III

CLOSING

6

SUMMARY AND DISCUSSION

In this thesis I have studied mechanisms how multiple internal models or motor memories are learned. I focused on how the brain reduces interference between multiple motor memories and also on how these memories generalize. In **chapter 2**, we showed that learning multiple internal models is possible if each is associated with a unique vestibular signal, serving as a contextual cue. Using a standard *ABA* paradigm, we showed faster relearning in the second exposure block compared to the first perturbation. We suggest that the vestibular signal helped in distinguishing between the two perturbing environments and thus helped to reduce interference between the associated internal models. In **chapter 3**, we investigated the generalization properties of a pre-movement serving as a contextual cue. First, we confirmed the findings of Howard et al. (2012), showing that simultaneous learning of two internal models is possible if both are linked to their own pre-movement direction. Next we focused on the generalization of these pre-movement cues and found that individual pre-movement cues generalize in a Gaussian-like fashion around the trained pre-movement direction. Furthermore, it was also shown that this pattern of generalization transfers to the untrained hand, irrespective of whether the trained hand was the dominant or the non-dominant hand. If only a single pre-movement cue to force field association was trained, a different generalization pattern arises, showing a combination of a global (offset) and local (Gaussian-like) generalization. These results suggest that a contextual cue does not operate as a binary selection mechanism, but rather as a weighting mechanism, determining which combination of the learnt internal models to use. In **chapter 4**, we investigated the underlying cause of interference between memories in standard *ABA* learning paradigms. It has been generally assumed that the lack of faster relearning occurs because memory *B* replaces memory *A* (erasure hypothesis). However, it is also possible that

both memories coexist, but that the lack of faster relearning is caused by the wrong memory being expressed (masking hypothesis). We used the spatial generalization of each memory as their unique fingerprints to distinguish between these two hypotheses. We found that traces of memory *A* were present in memory *B*'s generalization curve. This suggests that memory *A* is not replaced by *B* and that the lack of faster relearning is caused by a masking mechanism rather than by erasure. In **chapter 5**, we studied changes in the encoding and adaptation mechanisms when updating two internal models. To this end we manipulated the amount of interference between two opposing perturbations. We showed that learning two internal models simultaneously, each associated with their own target, is possible if the angular distance between targets is large enough. If targets become closer, learning deteriorates because interference levels increase. We used a "motor primitives" model to interpret both the learning and generalization data and showed that the deterioration in learning is directly linked to the extent of overlap between the generalization patterns of the two internal models. We also showed that by increasing interference levels the tuning of the underlying motor primitives becomes narrower. Furthermore, the learning mechanism, i.e. the updating of the primitives' weights, systematically changed from motion-referenced to plan-referenced with increasing levels of interference. We suggested that both mechanisms, narrower tuning and shift from motion to plan-referenced learning, occurs to combat increased levels of interference.

Next follows a more detailed summary of the **chapters 2-5**. This is followed by a discussion of the key findings and outlook of further research.

DETAILED SUMMARY

Chapter 2 - Vestibular benefits to task savings in motor adaptation

In everyday life, we seamlessly adapt our movements and consolidate them to multiple behavioral contexts. This natural flexibility seems to

be contingent on the presence of movement-related sensorimotor cues and cannot be reproduced when static visual or haptic cues are given to signify different behavioral contexts. So far, only sensorimotor cues that dissociate the sensorimotor plans prior to force field exposure have been successful in learning two opposing perturbations. In **chapter 2** we show that vestibular cues, which are only available during the perturbation, improve the formation and recall of multiple control strategies. We exposed subjects to inertial forces by accelerating them laterally on a vestibular platform. The coupling between reaching movement (forward-backward) and acceleration direction (leftward-rightward) switched every 160 trials, resulting in two opposite force environments. When exposed for a second time to the same environment, with the opposite environment in between, subjects showed retention resulting in an approximately three times faster adaptation rate compared to the first exposure. Our results suggest that vestibular cues provide contextual information throughout the reach, which is used to facilitate independent learning and recall of multiple motor memories. Vestibular cues provide feedback about the underlying cause of reach errors, thereby disambiguating the various task environments and reducing interference of motor memories.

Chapter 3 - Generalization and transfer of contextual cues in motor learning

We continuously adapt our movements in daily life, forming new internal models and updating existing ones whenever necessary. Recent work has suggested that this flexibility is enabled via sensorimotor cues, serving to access the correct internal model whenever necessary and keeping new models apart from previous ones. While research to date has mainly focused on identifying the nature of such cue representations, in this chapter we investigated whether and how these cue representations generalize, interfere, and transfer within and across effector systems. Subjects were trained to make two-stage reaching movements: a pre-movement that served as a cue, followed by a targeted movement that was perturbed by one of two opposite curl force fields. The direc-

tion of the pre-movement was uniquely coupled to the direction of the ensuing force field, enabling simultaneous learning of the two respective internal models. After training, generalization of the two pre-movement cues' representations was tested at untrained pre-movement directions, within both the trained and untrained hands. We show that the individual pre-movement representations generalize in a Gaussian-like pattern around the trained pre-movement direction. When the force fields are of unequal strengths, the cue-dependent generalization skews toward the strongest field. Furthermore, generalization patterns transfer to the non-trained hand, in an extrinsic reference frame. We conclude that contextual cues do not serve as discrete switches between multiple internal models. Instead, their generalization suggests a weighted contribution of the associated internal models based on the angular separation from the trained cues to the net motor output.

Chapter 4 - Masking and unmasking of human motor memories

Current research in memory suggests that during the acquisition of a memory, old memories are preserved in a latent form. For example, in fear research extinction learning successfully suppresses fear memories, but in situations of stress the fear memory reappears. This indicates that the original fear memory was only masked, not erased. Contrary to this model, the dominant view in motor learning is that old memories are erased, not masked, when acquiring a new motor memory. Does this mean that motor learning is a special form of learning, relying on different mechanisms than other memory systems? To come to an answer, we exploited the spatial generalization of force-field motor learning – the effect of the learning on targets other than the training direction. We make use of the fact that the spatial generalization of each memory is different and therefore can serve as its signature. We demonstrate that traces of a previously acquired motor memory remain visible in the spatial generalization of a newer motor memory, supporting a masking mechanism. These effects are visible if two successive memories are acquired at the same or different target directions. Our results suggest

that old motor memories are not erased, but masked when learning new memories, pointing toward a fundamental unifying mechanism across memory systems.

Chapter 5 - Flexible tuning and updating of motor primitives to reduce motor interference

Motor learning is thought to operate through the formation and adjustment of internal models of our body and the environment. The acquired internal models are not restricted to the learnt conditions alone but generalize to similar unexperienced conditions, interfering which each other at overlapping dimensions. The acquisition, generalization and interference of internal models has been interpreted in term of populations of motor primitives, whose output is determined by the updating of the primitives' weights, with ongoing debate whether these weight updates take place relative to the planned or actual motion. It has been suggested that not only primitives' weights are adjusted but that also their tuning can be flexible. However, are only weights and tuning width adjustable or can the updating mechanism change as well to meet task demands? Here we demonstrate that different levels of interference between opposite internal models induces changes in the spatial tuning of motor primitives and the reference frame in which internal model updating takes place (plan or motion-referenced learning). Human subjects performed reaching movements to two different targets, which were associated with opposite force fields. Different groups adapted to both force fields simultaneously, while the degree of target separation differed between groups. We found that both the learning rate and final adaptation level deteriorated as the targets became closer. At the same time, generalization narrowed and the peak of the generalization curves shifted. We modeled these observations using a motor primitives approach. Results indicate that to reduce interference between internal models for close target directions, primitives' tuning width decreases and the weight updating shifts from motion to plan-referenced. This challenges a strict division between plan and motion-referenced learning. Rather, a flexible

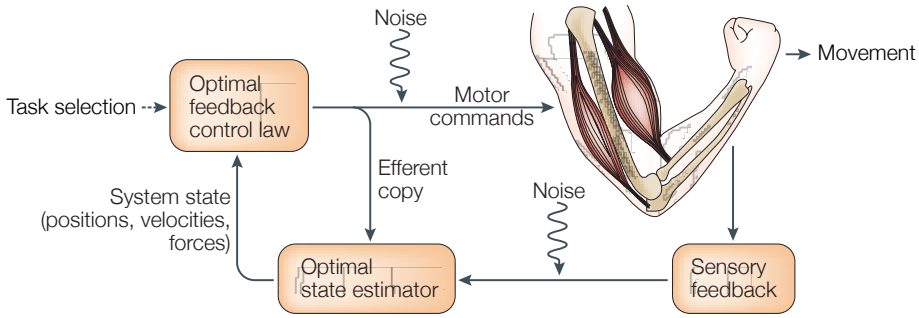


Figure 6.1: Optimal feedback control framework. Adapted from Scott (2004)

mechanism is at play, which adjusts the updating depending on the task requirements. The mechanism that causes these adjustments remains to be discovered.

DISCUSSION

I will discuss and synthesize the key findings of the experimental chapters to understand their further implications and make suggestions for further research.

What defines a contextual cue?

In **chapter 2**, we suggest that the vestibular system provides valuable contextual information and in **chapter 3** we showed the effectiveness, generalization and transfer of a contextual pre-movement cue (Howard et al., 2012). Especially the vestibular cue is a new addition to the collection of contextual cues. This raises the question what determines an effective contextual cue in motor learning? Why does static visual information like color not aid in learning multiple internal models, while vestibular cues and pre-movements do? Our suggestion is that only contextual cues that are part of the sensorimotor loop aid in learning mul-

tiple internal models. I will argue that optimal feedback control (OFC) provides a good framework for understanding.

When researchers first thought about the nature of a contextual cue, it was supposed that the information needed to be 'explicit', such as static visual or haptic cues (Gandolfo et al., 1996; Miall et al., 2004). In other words, it was assumed that subjects needed to be consciously aware of the contextual cue information. In the OFC scheme (figure 6.1), this would mean that the contextual cue is the input to the 'Task selection' component. However, explicit cues as such have been shown to be ineffective in learning multiple internal models (Gandolfo et al., 1996), suggesting that these cues do not define the task selection component in OFC. Rather, I suggest that the cue is part of the sensorimotor loop in this scheme. In OFC, sensory feedback is integrated with the internal estimate from which optimal feedback gains are determined. These feedback gains are adjustments to motor commands given the system's state. Feedback gains only exist for task-related sensory information and thus sensory information that does not contribute to the task is ignored.

Task-related sensory information is involved in dynamic state estimation. Static color cues on the one hand do not contribute in state estimation and as a result do not aid in learning internal models. Dynamic visual cues, like peripheral visual motion, on the other hand provide important information for state estimation, if directly coupled with each specific force field, and therefore aid in learning. Importantly, this allows for a possible explanation within the OFC framework and does not require incorporation of an arbitrary contextual cue switch (Lee and Schweighofer, 2009).

Is there a continuous spectrum of cue effectiveness?

If the OFC framework determines the value or gain of a sensory signal by which it is used as a contextual cue, then the effectiveness of contextual cues must follow a continuous scale. In other words, there is no binary distinction between effective and ineffective cues. Instead, there must be

a continuum regarding cue effectiveness, which may be based on the value of provided information for state estimation.

Support for this idea comes from a study that systematically investigated the effectiveness of different contextual cues in learning two internal models (Howard et al., 2013). That study showed that there is no discrete switch between cues that work and cues that do not. For example, peripheral visual motion aided in learning two internal models, but was less effective than visual object orientation, which in turn was less effective than the visual feedback location. To alter visual feedback location, proprioceptive space was kept the same across force fields, whereas the visual feedback was provided in separate workspaces. It would be interesting to find out where in the hyperspace of contextual cues the vestibular cue, reported in **chapter 2**, has a place?

Preliminary data from a recent study in our lab using galvanic vestibular stimulation (GVS), provide a glimpse on the effectiveness of vestibular cues. The advantage of GVS, compared to the setup in **chapter 2**, which employs whole-body displacements, is that the vestibular system can be singled out. In other words, only the vestibular system can be active, whereas during passive whole body movements other sensory signals could also provide cues, for example proprioception. In this new study, a pre-movement paradigm was used, similar to the one in **chapter 3**, which accompanied by brief galvanic vestibular stimulation (GVS) during the pre-movement. The direction of the velocity dependent GVS current during the pre-movement was coupled to the direction of the upcoming force field. The preliminary data suggest that subjects can learn two force fields simultaneously using the GVS as a cue. However, the magnitude of learning is substantially lower compared to single force field learning (Izawa et al., 2008). According to the new data, subjects attained about 30% of force compensation at the end of learning, whereas in single force field learning subjects attain about 80% (Izawa et al., 2008).

This provides additional evidence for a vestibular signal to work as a cue, but also suggests it might not be the best cue possible. In comparison with the study from **chapter 2**, the vestibular signal was provided during the perturbed reach execution, whereas in the recent pilot study the vestibular information was provided during the pre-movement. The

difference in timing might also change the value of information carried by the vestibular signal itself, which could result in different feedback gains.

Finding the neuronal correlates of contextual cues

Several contextual cues that contribute to learning multiple internal models have been identified in behavioral paradigms. However, it is still unknown where and how these cues are encoded in the brain.

Brain imaging techniques such as fMRI provide a tool that can help in identifying the possible anatomical location and the neurophysiology involved in coding contextual cues. I propose to use a paradigm that separates a motor planning period from a movement execution period. I also propose then to use visuomotor rotations as perturbation, which are easier to accommodate in a scanner environment than force fields.

As to the contextual cue in an fMRI environment, natural vestibular cues are hard to attain because recording purposes permit that one moves the head. GVS could potentially be tested, but distorts the magnetic field and therefore corrupts the BOLD signal. One possible alternative to vestibular cues using GVS, is MRI compatible caloric vestibular stimulation (CSV) (Frank and Greenlee, 2014). This technique elicits the perception of self motion by pumping water of different temperatures into one or both ear canals.

The pre-movements used in the experiments from **chapter 3** involve the execution of an actual movement. In an imaging experiment this would complicate the interpretation because the encoding of the pre-movement itself and its interpretation as a contextual cue are in dissociable. However, the original study by Howard et al. (2012) also contained an experimental paradigm in which there was no actual pre-movement executed. Instead a visual cursor moved, executing the pre-movement, to the via-point. At the same time the subject had her hand already at the via-point waiting for the pre-movement cursor to reach the via-point to then execute the perturbed reach. Also in this paradigm, two internal models could be acquired simultaneously. The advantage of this

paradigm is that the pre-movement is not actually executed but still provides valuable contextual information.

However, one problem still remains: execution of the perturbed movement is still required. To separate the planning and execution phases even more in time, it is possible to wait at the via-point for up to 0.6 seconds for the pre-movement to still act as a valuable cue (Howard et al., 2012). Despite this extended separation of planning and execution, the acquired BOLD signal in fMRI has a low temporal resolution. This could still result in the signal from the pre-movement to be overshadowed by the executed perturbed movement. Here MEG could be used, which offers much higher temporal resolution.

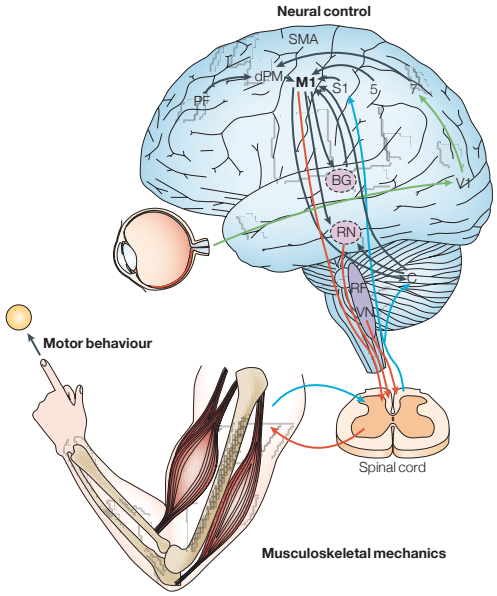
Using this paradigm of a cursor executed pre-movement, could shed light onto the broad neurophysiology of contextual cue coding in motor learning. The perturbed movement still needs to be executed, but in this context may be of less interest than the neurophysiological origin of contextual cue coding itself.

It is anyhow important to find out whether motor memories involve different brain areas than those usually identified in other memory research, such as the hippocampus. If so, then the probability of common features might be seen as pointing more towards common mechanisms throughout the brain.

BOX 1: BRAIN STRUCTURES INVOLVED IN OFC

The computations suggested within optimal feedback control (OFC) have been assigned to particular brain structures. One main part, the feedback controller (control policy), which sends out motor commands, resulting in a movement, has been related to the primary motor cortex (M1). The primary motor cortex is connected to the spinal cord, which controls muscle contractions. Electrical stimulation of M1 directly results in specific muscle contractions, for example in the hand. There has been debate whether M1 codes for muscle activ-

ity or movement. Patterns of activity in M1 relate its functionality to both (Scott, 2003).



This could be explained by the involvement of an internal model, where M1 acts like an inverse model. The output signals from an inverse model can reflect both direct muscle commands and global movement parameters such as velocity, position etc. To be able to act as an optimal feedback controller, M1 needs to receive a vast amount of sensory feedback. Research has shown that brain regions like the primary somatosensory cortex, posterior parietal cortex, and the cerebellum directly connect to M1 (Porter and Lemon, 1995).

The primary somatosensory cortex (S1) is the area that receives peripheral sensory information, reflecting y in the OFC figure from chapter 1. The cerebellum on the other hand has been shown to be crucial in learning new internal models (x^*).

The posterior parietal cortex (PPC) is involved in sensory integration ($\hat{x}$) planning of movement but also in online control (Desmurget et al., 1999; Cohen and Andersen, 2002; Gréa et al., 2002).

There are many more brain areas involved in movement planning and execution, which are crucial for specific aspects of movement. However, these have so far not been placed specifically within the OFC framework.

Brain areas and their connections involved in goal-directed reaching movements, from Scott (2004). **M1**, primary motor cortex; **S1**, primary somatosensory cortex; **5**, parietal cortex area 5; **7**, parietal cortex area 7; **BG**, basal ganglia; **C**, cerebellum; **RN**, red nucleus; **V1**, primary visual cortex; **dPM**, dorsal premotor cortex; **SMA**, supplementary motor area; **PF**, prefrontal cortex; **RF**, reticular formation; **VN**, vestibular nuclei.

Internal models in memory research

Motor learning has classically not been considered as part of general memory research. In this thesis we suggest that motor memories via internal models can provide a valuable asset for memory research in general. The advantage of motor memories is that they are clearly defined as a compensation strategy. This allows to track their acquisition over time. For "classic" memory tests like using a word list, this is much harder. First it is hard to measure its acquisition on a continuous scale; second and more importantly, what comprises a memory of a word list: is it a word, a group of words, or the list itself?

An additional benefit of a motor memory is that properties like generalization can be studied and manipulated through interference. The output of the memory can be probed in multiple dimensions (direction, position, velocity, force) and across time, which provides much richer information than a simple yes/no response. A further advantage is that motor memories are very similar across humans. This allows robust data collection, inferences based on relatively small datasets and good repro-

ducibility across the population. These advantages can be exploited in behavioral experiments, when combined with models of memory from a systems perspective.

Masking in other memory systems

In **chapter 4** we used the generalization properties of individual internal models as their fingerprints. These fingerprints allowed to distinguish between the erasure and masking hypothesis as the cause of the lack of faster relearning in *ABA* paradigms. In how far can a similar approach, using generalization properties, be adopted in other memory research?

The key ingredient for studying masking and erasure was the fact that motor memories generalize. What would generalization look like in a simple conditioning experiment? It is important to remember that generalization refers to the act of responding to a stimulus similar but distinct from the trained stimulus. The dimension along which the stimulus is modulated can be almost anything. In a tone-based eye blink conditioning experiment, for example, the dimension of generalization could be the pitch of the tone. When assessing generalization in a simple eye blink conditioning experiment the conditioned response is either present or absent in a single trial. This is in contrast to force field learning, where generalization is measured in terms of the amount of force, which exists on a continuous scale. So in an eye blink condition experiment one would have to adopt a psychometric approach to quantify generalization. This could be done using response frequencies in relation to changes along the pitch dimension.

In some ways, this is similar to experiment 2 of **chapter 4**, where the two force fields were associated with two different targets separated by 45°. After training each, generalization could be assessed as proposed via response frequency. The pattern within the response frequency can then also reveal possible masking.

Flexible neuronal properties

In **chapter 5**, we provided evidence that neuronal properties like tuning width are modulated to optimize learning multiple internal models. We argued that neuronal tuning sharpened to increase discriminability. Adaptation of neuronal tuning width has also been found in perception (Schoups et al., 2001; Teich and Qian, 2003) and attention (Spitzer et al., 1988; Lee et al., 1999) research. Evidence for a change in neuronal tuning is not limited to behavioral experiments but has been observed in single cell recordings (Gandolfo et al., 2000). Algorithmically, it has been suggested that this might work using a locally weighted projection regression (LWPR) model. This model is able to adjust its primitives' tuning width under altered task conditions. However, how and where this might be implemented in the brain remains an open question.

Another observation in chapter 5 was the shift of adaptation from motion-referenced to plan-referenced. This suggests that the learning mechanism itself is also flexible. But what kind of algorithm might cause such flexible shifts between reference frames? It is important to note that the shift from one learning mechanism to the other seemed to be based on the overlap of errors induced by the respective force fields. If opposite errors occur in the same workspace as in cases of high interference, error variance is high. This would also result in back and forth adjustment of motor primitives' weights. However, the assessment of error variance would require a memory of past errors, which was recently suggested to exist (Herzfeld et al., 2014). Next, a mechanism needs to be in place that reduces error variance by changing the weights that will be updated. It would be interesting to see if and how this algorithmic suggestion is implemented at a neuronal level.

CONCLUSION

Taken together, our results add to the understanding of internal models and the capability of humans to learn them. The approaches used in this study are on an algorithmic level (Marr, 1971). Further research is nec-

essary to investigate the implementation of the proposed computational processes. Unravelling these mechanisms does not only benefit fundamental neuroscience research, but can also aid in developing better skill learning methods in general or for the purpose of rehabilitation.

Part IV

APPENDIX

BIBLIOGRAPHY

Albert, N. B., Robertson, E. M., and Miall, R. C. (2009). The resting human brain and motor learning. *Current biology : CB*, 19(12):1023–1027. (Cited on page 94.)

Arce, F., Novick, I., Mandelblat-Cerf, Y., and Vaadia, E. (2010). Neuronal correlates of memory formation in motor cortex after adaptation to force field. *Journal of Neuroscience*, 30(27):9189–9198. (Cited on page 23.)

Atkeson, C. G. and Hollerbach, J. M. (1985). Kinematic features of unrestrained vertical arm movements. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 5(9):2318–2330. (Cited on page 6.)

Bakker, A., Kirwan, C. B., Miller, M., and Stark, C. E. L. (2008). Pattern separation in the human hippocampal CA3 and dentate gyrus. *Science*, 319(5870):1640–1642. (Cited on page 93.)

Berniker, M., Franklin, D. W., Flanagan, J. R., Wolpert, D. M., and Kording, K. (2014). Motor learning of novel dynamics is not represented in a single global coordinate system: evaluation of mixed coordinate representations and local learning. *Journal of Neurophysiology*, 111(6):1165–1182. (Cited on pages 11 and 78.)

Berniker, M. and Kording, K. (2008). Estimating the sources of motor errors for adaptation and generalization. *Nature Neuroscience*, 11(12):1454–1461. (Cited on page 47.)

Bernstein, N. A. (1967). *The Co-ordination and Regulation of Movements*. Pergamon Press. (Cited on page 3.)

Bouton, M. E. (2004). Context and behavioral processes in extinction. *Learning & memory (Cold Spring Harbor, N.Y.)*, 11(5):485–494. (Cited on page 92.)

Brashers-Krug, T., Shadmehr, R., and Bizzi, E. (1996). Consolidation in human motor memory. *Nature*, 382(6588):252–255. (Cited on pages 13, 30, 31, 42, 86, and 92.)

Brayanov, J. B., Press, D. Z., and Smith, M. A. (2012). Motor memory is encoded as a gain-field combination of intrinsic and extrinsic action representations. *Journal of Neuroscience*, 32(43):14951–14965. (Cited on page 106.)

Bresciani, J.-P., Gauthier, G. M., Vercher, J.-L., and Blouin, J. (2005). On the nature of the vestibular control of arm-reaching movements during whole-body rotations. *Experimental Brain Research*, 164(4):431–441. (Cited on page 46.)

Brock Kirwan, C., Hartshorn, A., Stark, S. M., Goodrich-Hunsaker, N. J., Hopkins, R. O., and Stark, C. E. L. (2012). Pattern separation deficits following damage to the hippocampus. *Neuropsychologia*, 50(10):2408–2414. (Cited on page 93.)

Caithness, G., Osu, R., Bays, P., Chase, H., Klassen, J., Kawato, M., Wolpert, D. M., and Flanagan, J. R. (2004). Failure to consolidate the consolidation theory of learning for sensorimotor adaptation tasks. *Journal of Neuroscience*, 24(40):8662–8671. (Cited on pages 12, 30, 31, 42, 46, 47, 48, 54, 86, and 92.)

Cherian, A., Fernandes, H. L., and Miller, L. E. (2013). Primary motor cortical discharge during force field adaptation reflects muscle-like dynamics. *Journal of Neurophysiology*, 110(3):768–783. (Cited on page 23.)

Chib, V. S., Patton, J. L., Lynch, K. M., and Mussa-Ivaldi, F. A. (2006). Haptic identification of surfaces as fields of force. *Journal of Neurophysiology*, 95(2):1068–1077. (Cited on page 49.)

Clemens, I. A. H., De Vrijer, M., Selen, L. P. J., Van Gisbergen, J. A. M., and Medendorp, W. P. (2011). Multisensory processing in spatial orientation: an inverse probabilistic approach. *Journal of Neuroscience*, 31(14):5365–5377. (Cited on page 47.)

Cohen, Y. E. and Andersen, R. A. (2002). A common reference frame for movement plans in the posterior parietal cortex. *Nature Reviews Neuroscience*, 3(7):553–562. (Cited on page 132.)

Colgin, L. L., Moser, E. I., and Moser, M.-B. (2008). Understanding memory through hippocampal remapping. *Trends in Neurosciences*, 31(9):469–477. (Cited on page 93.)

Coltz, J. D., Johnson, M. T., and Ebner, T. J. (1999). Cerebellar Purkinje cell simple spike discharge encodes movement velocity in primates during visuomotor arm tracking. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 19(5):1782–1803. (Cited on page 115.)

Conditt, M. A. and Mussa-Ivaldi, F. A. (1999). Central representation of time during motor learning. *Proceedings of the National Academy of Sciences of the United States of America*, 96(20):11625–11630. (Cited on page 34.)

Cothros, N., Wong, J., and Gribble, P. L. (2008). Distinct haptic cues do not reduce interference when learning to reach in multiple force fields. *PLoS ONE*, 3(4):e1990. (Cited on pages 13, 30, and 46.)

Crevecoeur, F., Thonnard, J.-L., and Lefèvre, P. (2009). Optimal integration of gravity in trajectory planning of vertical pointing movements. *Journal of Neurophysiology*, 102(2):786–796. (Cited on page 49.)

Crevecoeur, F., Thonnard, J.-L., and Lefèvre, P. (2010). Sensorimotor mapping for anticipatory grip force modulation. *Journal of Neurophysiology*, 104(3):1401–1408. (Cited on page 49.)

Criscimagna-Hemminger, S. E., Donchin, O., Gazzaniga, M. S., and Shadmehr, R. (2003). Learned dynamics of reaching movements generalize from dominant to nondominant arm. *Journal of Neurophysiology*, 89(1):168–176. (Cited on pages 55, 78, and 79.)

Criscimagna-Hemminger, S. E. and Shadmehr, R. (2008). Consolidation patterns of human motor memory. *The Journal of neuroscience : the*

official journal of the Society for Neuroscience, 28(39):9610–9618. (Cited on pages 30 and 48.)

Desmurget, M., Epstein, C. M., Turner, R. S., Prablanc, C., Alexander, G. E., and Grafton, S. T. (1999). Role of the posterior parietal cortex in updating reaching movements to a visual target. *Nature Neuroscience*, 2(6):563–567. (Cited on page 132.)

Diedrichsen, J., Shadmehr, R., and Ivry, R. B. (2010). The coordination of movement: optimal feedback control and beyond. *Trends in Cognitive Sciences*, 14(1):31–39. (Cited on page 7.)

Dizio, P. and Lackner, J. R. (1995). Motor adaptation to Coriolis force perturbations of reaching movements: endpoint but not trajectory adaptation transfers to the nonexposed arm. *Journal of Neurophysiology*, 74(4):1787–1792. (Cited on pages 31 and 55.)

Donchin, O., Francis, J. T., and Shadmehr, R. (2003). Quantifying generalization from trial-by-trial behavior of adaptive systems that learn with basis functions: theory and experiments in human motor control. *Journal of Neuroscience*, 23(27):9032–9045. (Cited on pages 11, 14, 19, 20, 54, 86, 100, 106, and 115.)

Ebner, T. J., Hewitt, A. L., and Popa, L. S. (2011). What Features of Limb Movements are Encoded in the Discharge of Cerebellar Neurons? *The Cerebellum*, 10(4):683–693. (Cited on pages 22 and 94.)

Flash, T. and Hogan, N. (1985). The coordination of arm movements: an experimentally confirmed mathematical model. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 5(7):1688–1703. (Cited on page 6.)

Frank, S. M. and Greenlee, M. W. (2014). An MRI-compatible caloric stimulation device for the investigation of human vestibular cortex. *Journal of Neuroscience Methods*, 235:208–218. (Cited on page 129.)

Franklin, D. W., Osu, R., Burdet, E., Kawato, M., and Milner, T. E. (2003). Adaptation to stable and unstable dynamics achieved by combined

impedance control and inverse dynamics model. *Journal of Neurophysiology*, 90(5):3270–3282. (Cited on pages 37, 38, 61, 87, and 96.)

Franklin, D. W. and Wolpert, D. M. (2008). Specificity of reflex adaptation for task-relevant variability. *Journal of Neuroscience*, 28(52):14165–14175. (Cited on pages 11, 56, and 103.)

Franklin, D. W. and Wolpert, D. M. (2011). Computational mechanisms of sensorimotor control. *Neuron*, 72(3):425–442. (Cited on page 5.)

Galea, J. M., Miall, R. C., and Woolley, D. G. (2007). Asymmetric interlimb transfer of concurrent adaptation to opposing dynamic forces. *Experimental Brain Research*, 182(2):267–273. (Cited on page 55.)

Galea, J. M., Vazquez, A., Pasricha, N., de Xivry, J.-J. O., and Celnik, P. (2011). Dissociating the roles of the cerebellum and motor cortex during adaptive learning: the motor cortex retains what the cerebellum learns. *Cerebral Cortex*, 21(8):1761–1770. (Cited on pages 22, 94, and 115.)

Gandolfo, F., Li, C., Benda, B. J., Schioppa, C. P., and Bizzi, E. (2000). Cortical correlates of learning in monkeys adapting to a new dynamical environment. *Proceedings of the National Academy of Sciences of the United States of America*, 97(5):2259–2263. (Cited on pages 114 and 134.)

Gandolfo, F., Mussa-Ivaldi, F. A., and Bizzi, E. (1996). Motor learning by field approximation. *Proceedings of the National Academy of Sciences of the United States of America*, 93(9):3843–3846. (Cited on pages 13, 30, 46, 54, 86, and 127.)

Ghahramani, Z. and Wolpert, D. M. (1997). Modular decomposition in visuomotor learning. *Nature*, 386(6623):392–395. (Cited on pages 54 and 81.)

Gonzalez Castro, L. N., Monsen, C. B., and Smith, M. A. (2011). The binding of learning to action in motor adaptation. *PLoS Computational Biology*, 7(6):e1002052. (Cited on pages 20, 21, 100, and 115.)

Gréa, H., Pisella, L., Rossetti, Y., Desmurget, M., Tilikete, C., Grafton, S., Prablanc, C., and Vighetto, A. (2002). A lesion of the posterior parietal cortex disrupts on-line adjustments during aiming movements. *Neuropsychologia*, 40(13):2471–2480. (Cited on page 132.)

Harris, C. M. and Wolpert, D. M. (1998). Signal-dependent noise determines motor planning. *Nature*, 394(6695):780–784. (Cited on page 6.)

Haruno, M., Wolpert, D. M., and Kawato, M. (2001). Mosaic model for sensorimotor learning and control. *Neural computation*, 13(10):2201–2220. (Cited on page 81.)

Herzfeld, D. J., Vaswani, P. A., Marko, M. K., and Shadmehr, R. (2014). A memory of errors in sensorimotor learning. *Science*, 345(6202):1349–1353. (Cited on pages 79 and 134.)

Hirashima, M. and Nozaki, D. (2012). Distinct motor plans form and retrieve distinct motor memories for physically identical movements. *Current biology : CB*, 22(5):432–436. (Cited on pages 14, 30, 46, 47, 48, and 54.)

Howard, I. S. and Franklin, D. W. (2015). Neural Tuning Functions Underlie Both Generalization and Interference. *PLoS ONE*, 10(6):e0131268. (Cited on page 78.)

Howard, I. S., Ingram, J. N., Franklin, D. W., and Wolpert, D. M. (2012). Gone in 0.6 seconds: the encoding of motor memories depends on recent sensorimotor states. *Journal of Neuroscience*, 32(37):12756–12768. (Cited on pages 14, 30, 46, 47, 48, 54, 55, 73, 76, 93, 121, 126, 129, and 130.)

Howard, I. S., Ingram, J. N., and Wolpert, D. M. (2008). Composition and decomposition in bimanual dynamic learning. *Journal of Neuroscience*, 28(42):10531–10540. (Cited on pages 30, 47, and 48.)

Howard, I. S., Ingram, J. N., and Wolpert, D. M. (2009). A modular planar robotic manipulandum with end-point torque control. *Journal of Neuroscience Methods*, 181(2):199–211. (Cited on pages 9, 87, and 102.)

Howard, I. S., Ingram, J. N., and Wolpert, D. M. (2010). Context-dependent partitioning of motor learning in bimanual movements. *Journal of Neurophysiology*, 104(4):2082–2091. (Cited on pages 30, 47, and 48.)

Howard, I. S., Wolpert, D. M., and Franklin, D. W. (2013). The effect of contextual cues on the encoding of motor memories. *Journal of Neurophysiology*, 109(10):2632–2644. (Cited on page 128.)

Howard, I. S., Wolpert, D. M., and Franklin, D. W. (2015). The value of the follow-through derives from motor learning depending on future actions. *Current biology : CB*, 25(3):397–401. (Cited on page 14.)

Hunsaker, M. R. and Kesner, R. P. (2013). The operation of pattern separation and pattern completion processes associated with different attributes or domains of memory. *Neuroscience & Biobehavioral Reviews*, 37(1):36–58. (Cited on page 93.)

Hwang, E. J., Smith, M. A., and Shadmehr, R. (2006a). Adaptation and generalization in acceleration-dependent force fields. *Experimental Brain Research*, 169(4):496–506. (Cited on pages 47 and 49.)

Hwang, E. J., Smith, M. A., and Shadmehr, R. (2006b). Dissociable effects of the implicit and explicit memory systems on learning control of reaching. *Experimental Brain Research*, 173(3):425–437. (Cited on pages 14 and 30.)

Ingram, J. N., Flanagan, J. R., and Wolpert, D. M. (2013). Context-Dependent Decay of Motor Memories during Skill Acquisition. *Current biology : CB*, 23(12):1107–1112. (Cited on page 106.)

Izawa, J., Criscimagna-Hemminger, S. E., and Shadmehr, R. (2012). Cerebellar contributions to reach adaptation and learning sensory consequences of action. *Journal of Neuroscience*, 32(12):4230–4239. (Cited on pages 11, 54, 86, and 100.)

Izawa, J., Rane, T., Donchin, O., and Shadmehr, R. (2008). Motor adaptation as a process of reoptimization. *Journal of Neuroscience*, 28(11):2883–2891. (Cited on pages 30, 40, 49, and 128.)

Joiner, W. M., Brayanov, J. B., and Smith, M. A. (2013). The training schedule affects the stability, not the magnitude, of the interlimb transfer of learned dynamics. *Journal of Neurophysiology*, 110(4):984–998. (Cited on pages 55 and 78.)

Karniel, A. and Mussa-Ivaldi, F. A. (2003). Sequence, time, or state representation: how does the motor control system adapt to variable environments? *Biological cybernetics*, 89(1):10–21. (Cited on page 34.)

Kawato, M. (1999). Internal models for motor control and trajectory planning. *Current Opinion in Neurobiology*, 9(6):718–727. (Cited on page 30.)

Kitazawa, S., Kimura, T., and Yin, P. B. (1998). Cerebellar complex spikes encode both destinations and errors in arm movements. *Nature*, 392(6675):494–497. (Cited on page 115.)

Krakauer, J. W., Ghez, C., and Ghilardi, M. F. (2005). Adaptation to visuomotor transformations: Consolidation, interference, and forgetting. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 25(2):473–478. (Cited on pages 9, 12, 46, and 93.)

Krakauer, J. W., Pine, Z. M., Ghilardi, M. F., and Ghez, C. (2000). Learning of visuomotor transformations for vectorial planning of reaching trajectories. *Journal of Neuroscience*, 20(23):8916–8924. (Cited on page 106.)

Krekelberg, B., van Wezel, R. J. A., and Albright, T. D. (2006). Adaptation in macaque MT reduces perceived speed and improves speed discrimination. *Journal of Neurophysiology*, 95(1):255–270. (Cited on page 114.)

Lackner, J. R. and Dizio, P. (1994). Rapid adaptation to Coriolis force perturbations of arm trajectory. *Journal of Neurophysiology*, 72(1):299–313. (Cited on page 31.)

Lackner, J. R. and Dizio, P. (1998). Gravitoinertial force background level affects adaptation to Coriolis force perturbations of reaching movements. *Journal of Neurophysiology*, 80(2):546–553. (Cited on pages 49 and 50.)

Lacy, J. W., Yassa, M. A., Stark, S. M., Muftuler, L. T., and Stark, C. E. L. (2011). Distinct pattern separation related transfer functions in human CA3/dentate and CA1 revealed using high-resolution fMRI and variable mnemonic similarity. *Learning & memory (Cold Spring Harbor, N.Y.)*, 18(1):15–18. (Cited on page 93.)

Lee, D. K., Itti, L., Koch, C., and Braun, J. (1999). Attention activates winner-take-all competition among visual filters. *Nature Neuroscience*, 2(4):375–381. (Cited on pages 114 and 134.)

Lee, J.-Y. and Schweighofer, N. (2009). Dual adaptation supports a parallel architecture of motor memory. *Journal of Neuroscience*, 29(33):10396–10404. (Cited on pages 14, 17, 48, 81, and 127.)

Li, C. S., Padoa-Schioppa, C., and Bizzi, E. (2001). Neuronal correlates of motor performance and motor learning in the primary motor cortex of monkeys adapting to an external force field. *Neuron*, 30(2):593–607. (Cited on page 23.)

Malone, L. A., Vasudevan, E. V. L., and Bastian, A. J. (2011). Motor Adaptation Training for Faster Relearning. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 31(42):15136–15143. (Cited on pages 30 and 47.)

Manoach, D. S., Cain, M. S., Vangel, M. G., Khurana, A., Goff, D. C., and Stickgold, R. (2004). A failure of sleep-dependent procedural learning in chronic, medicated schizophrenia. *Biological Psychiatry*, 56(12):951–956. (Cited on page 93.)

Marongelli, E. N. and Thoroughman, K. A. (2013). The advantage of flexible neuronal tunings in neural network models for motor learning. *Frontiers in computational neuroscience*, 7:100. (Cited on page 114.)

Marr, D. (1971). Simple memory: a theory for archicortex. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 262(841):23–81. (Cited on pages 94 and 134.)

Martin, T. A., Keating, J. G., Goodkin, H. P., Bastian, A. J., and Thach, W. T. (1996a). Throwing while looking through prisms. I. Focal olivocerebellar lesions impair adaptation. *Brain : a journal of neurology*, 119 (Pt 4):1183–1198. (Cited on page 22.)

Martin, T. A., Keating, J. G., Goodkin, H. P., Bastian, A. J., and Thach, W. T. (1996b). Throwing while looking through prisms. II. Specificity and storage of multiple gaze-throw calibrations. *Brain : a journal of neurology*, 119 (Pt 4):1199–1211. (Cited on page 22.)

Maschke, M., Gomez, C. M., Ebner, T. J., and Konczak, J. (2004). Hereditary cerebellar ataxia progressively impairs force adaptation during goal-directed arm movements. *Journal of Neurophysiology*, 91(1):230–238. (Cited on pages 11, 86, and 100.)

Mattar, A. A. G. and Ostry, D. J. (2010). Generalization of dynamics learning across changes in movement amplitude. *Journal of Neurophysiology*, 104(1):426–438. (Cited on page 54.)

Miall, R. C., Christensen, L. O. D., Cain, O., and Stanley, J. (2007). Disruption of state estimation in the human lateral cerebellum. *PLoS Biology*, 5(11):e316. (Cited on pages 22 and 94.)

Miall, R. C., Jenkinson, N., and Kulkarni, K. (2004). Adaptation to rotated visual feedback: a re-examination of motor interference. *Experimental Brain Research*, 154(2):201–210. (Cited on pages 12, 13, 49, and 127.)

Milner, B. (1962). Les troubles de la memoire accompagnant des lesions hippocampiques bilaterales. *Physiologie de l'hippocampe*, page 257–272. (Cited on page 93.)

Milner, B., Squire, L. R., and Kandel, E. R. (1998). Cognitive neuroscience and the study of memory. *Neuron*, 20(3):445–468. (Cited on page 93.)

Morasso, P. (1981). Spatial control of arm movements. *Experimental Brain Research*, 42(2):223–227. (Cited on page 6.)

Nader, K. (2003). Memory traces unbound. *Trends in Neurosciences*, 26(2):65–72. (Cited on page 48.)

Nader, K., Schafe, G. E., and LeDoux, J. E. (2000). The labile nature of consolidation theory. *Nature Reviews Neuroscience*, 1(3):216–219. (Cited on page 48.)

Nozaki, D., Kurtzer, I., and Scott, S. H. (2006). Limited transfer of learning between unimanual and bimanual skills within the same limb. *Nature Neuroscience*, 9(11):1364–1366. (Cited on pages 30, 47, and 48.)

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, 9(1):97–113. (Cited on pages 56 and 102.)

Osu, R., Hirai, S., Yoshioka, T., and Kawato, M. (2004). Random presentation enables subjects to adapt to two opposing forces on the hand. *Nature Neuroscience*, 7(2):111–112. (Cited on page 46.)

Paz, R. and Vaadia, E. (2004). Learning-induced improvement in encoding and decoding of specific movement directions by neurons in the primary motor cortex. *PLoS Biology*, 2(2):E45. (Cited on page 114.)

Pekny, S. E., Criscimagna-Hemminger, S. E., and Shadmehr, R. (2011). Protection and expression of human motor memories. *Journal of Neuroscience*, 31(39):13829–13839. (Cited on pages 13, 14, 30, 48, and 93.)

Poggio, T. and Bizzi, E. (2004). Generalization in vision and motor control. *Nature*, 431(7010):768–774. (Cited on pages 14, 19, 20, 54, 100, and 106.)

Porter, R. and Lemon, R. (1995). *Corticospinal Function and Voluntary Movement*. Oxford University Press. (Cited on page 131.)

Pouget, A. and Snyder, L. H. (2000). Computational approaches to sensorimotor transformations. *Nature Neuroscience*, 3 Suppl:1192–1198. (Cited on pages 14, 19, 20, 100, and 106.)

Sainburg, R. L. (2002). Evidence for a dynamic-dominance hypothesis of handedness. *Experimental Brain Research*, 142(2):241–258. (Cited on pages 79 and 80.)

Sarwary, A. M. E., Selen, L. P. J., and Medendorp, W. P. (2013). Vestibular benefits to task savings in motor adaptation. *Journal of Neurophysiology*, 110(6):1269–1277. (Cited on pages 54 and 93.)

Scheidt, R. A., Reinkensmeyer, D. J., Conditt, M. A., Rymer, W. Z., and Mussa-Ivaldi, F. A. (2000). Persistence of motor adaptation during constrained, multi-joint, arm movements. *Journal of Neurophysiology*, 84(2):853–862. (Cited on pages 10, 58, 89, 95, and 104.)

Schoups, A., Vogels, R., Qian, N., and Orban, G. (2001). Practising orientation identification improves orientation coding in V1 neurons. *Nature*, 412(6846):549–553. (Cited on pages 114 and 134.)

Scott, S. H. (2003). The role of primary motor cortex in goal-directed movements: insights from neurophysiological studies on non-human primates. *Current Opinion in Neurobiology*, 13(6):671–677. (Cited on page 131.)

Scott, S. H. (2004). Optimal feedback control and the neural basis of volitional motor control. *Nature Reviews Neuroscience*, 5(7):532–546. (Cited on pages 126 and 132.)

Shabbott, B. A. and Sainburg, R. L. (2008). Differentiating between two models of motor lateralization. *Journal of Neurophysiology*, 100(2):565–575. (Cited on page 80.)

Shadmehr, R. and Mussa-Ivaldi, F. A. (1994). Adaptive representation of dynamics during learning of a motor task. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 14(5 Pt 2):3208–3224. (Cited on pages 10, 30, 42, and 50.)

Shadmehr, R. and Wise, S. P. (2005). *The Computational Neurobiology Of Reaching And Pointing*. A Foundation for Motor Learning. The MIT Press. (Cited on page 30.)

Smith, M. A., Ghazizadeh, A., and Shadmehr, R. (2006). Interacting adaptive processes with different timescales underlie short-term motor learning. *PLoS Biology*, 4(6):e179. (Cited on pages 10, 14, 15, 17, 58, 89, 95, 104, and 106.)

Spitzer, H., Desimone, R., and Moran, J. (1988). Increased attention enhances both behavioral and neuronal performance. *Science*, 240(4850):338–340. (Cited on pages 114 and 134.)

Teich, A. F. and Qian, N. (2003). Learning and adaptation in a recurrent model of V1 orientation selectivity. *Journal of Neurophysiology*, 89(4):2086–2100. (Cited on pages 114 and 134.)

Thoroughman, K. A. and Shadmehr, R. (2000). Learning of action through adaptive combination of motor primitives. *Nature*, 407(6805):742–747. (Cited on pages 14, 19, 20, 54, 100, 106, and 115.)

Thoroughman, K. A. and Taylor, J. A. (2005). Rapid reshaping of human motor generalization. *Journal of Neuroscience*, 25(39):8948–8953. (Cited on pages 78, 100, 113, and 115.)

Todorov, E. and Jordan, M. I. (2002). Optimal feedback control as a theory of motor coordination. *Nature Neuroscience*, 5(11):1226–1235. (Cited on page 6.)

Uno, Y., Kawato, M., and Suzuki, R. (1989). Formation and control of optimal trajectory in human multijoint arm movement. Minimum torque-change model. *Biological cybernetics*, 61(2):89–101. (Cited on page 6.)

Wang, J. and Sainburg, R. L. (2004). Interlimb transfer of novel inertial dynamics is asymmetrical. *Journal of Neurophysiology*, 92(1):349–360. (Cited on page 55.)

Wilson, D. A. (2009). Pattern separation and completion in olfaction. *Annals of the New York Academy of Sciences*, 1170:306–312. (Cited on page 93.)

Wolpert, D. M., Diedrichsen, J., and Flanagan, J. R. (2011). Principles of sensorimotor learning. *Nature Reviews Neuroscience*. (Cited on page 16.)

Wolpert, D. M., Miall, R. C., and Kawato, M. (1998). Internal models in the cerebellum. *Trends in Cognitive Sciences*, 2(9):338–347. (Cited on pages 5 and 115.)

Wong, J. D., Wilson, E. T., Kistemaker, D. A., and Gribble, P. L. (2014). Bimanual proprioception: are two hands better than one? *Journal of Neurophysiology*, 111(6):1362–1368. (Cited on pages 77 and 80.)

Yokoi, A., Hirashima, M., and Nozaki, D. (2014). Lateralized sensitivity of motor memories to the kinematics of the opposite arm reveals functional specialization during bimanual actions. *Journal of Neuroscience*, 34(27):9141–9151. (Cited on pages 14, 18, 19, 20, 76, 81, 106, and 107.)

NEDERLANDSE SAMENVATTING

In dit proefschrift heb ik de mechanismen bestudeerd die ten grondslag liggen aan het vormen van het motorisch geheugen, in het bijzonder hoe meerdere interne motorische representaties worden gevormd en opgeslagen. Ik heb hierbij onderzocht hoe interferentie tussen motorische representaties geminimaliseerd kan worden en hoe motorische representaties generaliseren. Hieronder volgt een meer gedetailleerd overzicht van de bevindingen beschreven in hoofdstukken **2-5**. Ik sluit af met een algemene conclusie.

HOOFDSTUK 2: VESTIBULAIRE CONTEXT HELPT HET VORMEN EN ONDERSCHEIDEN VAN MOTORISCHE REPRESENTATIES

In het dagelijks leven passen wij onze bewegingen naadloos aan op veranderingen van ons lichaam of onze omgeving. Bovendien slaan we het geleerde op om het te gebruiken op latere momenten en in een andere gedragscontext. Hoe komt deze natuurlijke flexibiliteit tot stand? Eerder onderzoek liet zien dat contextuele cues, zoals statische visuele of haptische signalen, niet voldoen voor het differentiëren tussen meerdere motorische representaties. In **hoofdstuk 2** laat ik zien dat vestibulaire signalen, die alleen beschikbaar zijn tijdens de verstoring van de geplande beweging, het mogelijk maken om de motorische representaties voor twee tegengestelde verstoringen te vormen en terug te roepen. Proefpersonen werden zijdelings versneld op een vestibulair platform waardoor er traagheidskrachten op hun arm werkten tijdens de reikbeweging. De koppeling tussen de richting van de reikbewegingen (vooruit-achteruit) en zijdelingse versnellingen (links-rechts) veranderde elke 160 reikbewegingen, resulterend in twee tegengestelde verstoringsomgevingen, die elkaar opvolgden middels een ABAB paradigma. Bij de tweede blootstelling aan dezelfde omgeving B, met de omgeving A er tussenin,

toonden proefpersonen retentie resulterend in een ongeveer driemaal snellere aanpassing aan deze omgeving in vergelijking met de eerste blootstelling aan B. Deze resultaten tonen aan dat vestibulaire signalen contextuele informatie verschaffen over de verstoringsomgeving tijdens de hele reikbeweging. Op basis van deze contextuele informatie kunnen meerdere motorische representaties onafhankelijk van elkaar geleerd en aangeroepen worden. Vestibulaire signalen geven feedback over de onderliggende oorzaak van de reikfouten, waardoor de verstoringsomgevingen beter onderscheiden worden en interferentie tussen motorische representaties verminderd wordt.

HOOFDSTUK 3: GENERALISATIE EN OVERDRACHT VAN MOTORISCHE REPRESENTATIES OP BASIS VAN CONTEXTUELE SIGNALEN

In het dagelijks leven passen wij voortdurend onze bewegingen aan. Dit resulteert in de vorming van nieuwe en aanpassing van bestaande interne motorische representaties. Recente studies suggereren dat deze flexibiliteit mogelijk wordt gemaakt door sensomotorische signalen die helpen om nieuwe van oude interne modellen te scheiden. Tot op heden heeft het onderzoek zich vooral gericht op het identificeren van de aard van dergelijke contextuele cues. In **hoofdstuk 3** heb ik onderzocht of en hoe deze contextuele representaties generaliseren en interfereren binnen de reikbewegingen van een enkele arm en tussen reikbewegingen van beide armen. Hiertoe werden proefpersonen getraind om twee opeenvolgende reikbewegingen te maken met een haptisch manipulandum. De eerste reikbeweging was onverstoord en diende als het contextuele signaal, terwijl tijdens de tweede beweging een zijwaartse kracht op de hand werd uitgeoefend. Deze verstoring kon een van twee tegengestelde krachtenvelden zijn. De richting van de eerste beweging was voorspellend – een contextuele cue – voor de richting van het daaropvolgende krachtenveld. Op deze manier konden proefpersonen twee interne modellen gelijktijdig leren. Na het leren van de twee motorische representaties werd de generalisatie van de twee pre-bewegingscues onderzocht voor niet-getrainde richtingen, zowel voor de getrainde als de

ongetrainde hand. De resultaten tonen aan dat de individuele contextuele cues generaliseren volgens een Gaussisch patroon rond de geleerde richting van de pre-beweging. Wanneer de krachtenvelden van ongelijke sterkte zijn, schuift de context-afhankelijke generalisatie op in de richting van pre-beweging die geassocieerd is met het sterkste krachtenveld. Bovendien laten we zien dat het generalisatiepatroon in de getrainde hand ook tot uiting komt in de ongetrainde hand. Dit patroon is gecodeerd in een extrinsiek coördinatenstelsel. We concluderen dat contextuele cues niet als discrete schakelaars fungeren om verschillende interne modellen aan te roepen, maar gezamenlijk leiden tot de expressie van een gewogen bijdrage van de geassocieerde interne modellen, gebaseerd op de afstand tussen de getrainde contexten en de aangeboden pre-bewegingsrichting.

HOOFDSTUK 4: MASKEREN EN ONTMASKEREN VAN MOTORISCHE GEHEUGEN

Huidige theorieën over het geheugen suggereren dat tijdens de vorming van een nieuwe herinnering oude herinneringen worden bewaard in een latente vorm. Onderzoek naar angst laat bijvoorbeeld zien dat extinctie leren succesvol angstherinneringen onderdrukt, maar dat in situaties van stress deze herinnering zich toch opnieuw kan uiten. Dit geeft aan dat het oorspronkelijk angstgeheugen slechts was gemaskeerd en niet uitgewist. In tegenstelling tot dit gangbare model voor geheugenrepresentaties is de dominante visie in motorisch leren dat oude motorische representaties worden gewist bij het aanleren van een nieuwe motorische representatie. Betekent dit dat motorisch leren een bijzondere vorm van leren is, met andere leermechanismen dan voor de meeste geheugensystemen? Om deze vraag te beantwoorden hebben we gebruik gemaakt van de generalisatie rond de getrainde richting van een nieuwe motorische representatie van een verstorend krachtenveld – ofwel, het effect van een nieuwe motorische representatie op reikbewegingen in andere reikrichtingen dan de getrainde richting. Wij maakten gebruik van het feit dat deze ruimtelijke generalisatie voor elke motorische representatie

anders van vorm is en daarom kan dienen als signatuur van een specifieke representatie. We tonen aan dat sporen van een eerder verworven motorische representatie zichtbaar blijven in de ruimtelijke generalisatie van een later geleerde motorische representatie. Dit suggereert dat motorische representaties worden gemaskeerd en niet gewist. Deze effecten zijn zichtbaar als twee tegengestelde motorische representaties serieel worden geleerd voor dezelfde en voor verschillende reikrichtingen. Onze resultaten suggereren dat oude motorische representaties niet worden gewist maar gemaskeerd tijdens het leren van nieuwe representaties. Dit wijst in de richting van een fundamenteel mechanisme dat geldig is voor alle geheugensystemen.

HOOFDSTUK 5: MECHANISMEN VAN MOTORISCH LEREN EN GENERALISATIE

Motorisch leren wordt gedacht te werken door de vorming en aanpassing van interne modellen van ons lichaam en de omgeving. De verworven interne modellen beperken zich niet tot de geleerde condities maar generaliseren ook daarbuiten waar ze interfereren met naburige interne modellen. De vorming, generalisatie en interferentie van interne modellen wordt geïnterpreteerd in termen van de populaties van de motor primitieven, waarvan de output wordt bepaald door de gewichten van de primitieven. Er is debat of de aanpassing van de gewichten van deze primitieven plaatsvindt op basis van de geplande of de werkelijke beweging. Daarnaast is er gesuggereerd dat niet alleen de gewichten van de motor primitieven aangepast kunnen worden, maar ook de reikwijdte van de primitieven. In hoofdstuk 5 laten we zien dat de mate van interferentie tussen twee tegengestelde interne modellen veranderingen veroorzaakt in de reikwijdte van de motorische primitieven en de manier waarop hun gewichten worden aangepast. Met weinig interferentie tussen de interne modellen vindt de update plaats in relatie tot de geplande beweging, maar naarmate de interferentie toeneemt verschuift deze update richting de werkelijke beweging. Proefpersonen maakten reikbewegingen naar twee verschillende doelen, die gekoppeld waren

aan tegengestelde krachtenvelden. We varieerden de afstand tussen de twee doelen, en voor elke afstand werd een verschillende groep proefpersonen getest. We vonden dat zowel de snelheid van leren als ook de hoogte van het leerplateau afnamen als de doelen dichter bij elkaar lagen. Ook werd de generalisatiecurve smaller en verschoof de piek van de generalisatiecurves. We hebben deze waarnemingen gemodelleerd op basis van motor primitieven. Simulaties laten zien dat om interferentie tussen de interne modellen te verminderen als de doelen dichter bij elkaar liggen, de reikwijdte van de primitieven moet afnemen en dat de aanpassing van de gewichten van de primitieven verschuift van relatief ten opzichte van de gemaakte naar de geplande beweging. Dit heeft implicaties voor modellen die veronderstellen dat er een strikte scheiding bestaat tussen updating op basis van de geplande en de uitgevoerde beweging. Onze resultaten pleiten voor een flexibel mechanisme, waarin de gewichten van de motorische primitieven aanpast worden afhankelijk van de taak.

CONCLUSIE

Onze resultaten vergroten het computationele begrip van interne modellen en het vermogen van de mens om motorisch te leren. Verdere studie is nodig om de implementatie van de computationele processen te onderzoeken. Het ontrafelen van deze mechanismen komt niet alleen ten goede aan fundamenteel neurowetenschappelijk onderzoek, maar kan ook helpen bij het ontwikkelen van betere leermethoden in brede zin of voor het verbeteren van revalidatietechnieken gericht op het herstel van motorische vaardigheden.

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Pieter, I still remember the first time I met you. It was during the introduction day of the research master and the students got divided into small groups, one for each track (only three back then). Short presentations of the topics that were going to be covered by each teacher followed. You were talking about motor control, showing videos of animals that display amazing motor control. However, I honestly didn't really know back then what to make of it. The first motor control class changed everything for me. After that I asked you a bunch of questions and you even lent me the 'The computational neurobiology of reaching and pointing: a foundation for motor learning' book, the blue one – remember? I was hooked! From that point on I was always looking forward to the content of the motor control class, not the time it took place (very early in the morning). I still don't know how I managed to be on time throughout the entire semester.

One of the classes was taught by **Luc**. Adaptation!! That's all it was about and I have to say that topic even after 5 years is still incredibly interesting to me. After you two have agreed to have me as an intern for the end of my masters I couldn't have been happier. **Luc**, you made sure to show me how challenging this was going to be. First day, I was there at 9am in the morning and you (**Luc**) were late. As we have experienced that was the only time for the years to come when you were late and I was on time. Well, maybe it happened 3-4 times more. However, you were telling me a lot about OFC (optimal feedback control). Something I have never ever heard anything about and you only kept on throwing

jargon at me. I thought first thing is to understand the jargon in detail. Point 1: the Kalman filter... Hours later you found me in the end in the CNS computer room and gave me a little pep talk. Much appreciated!

From there on, you two were basically telling me that you were at my constant beck and call, also known as the 'open door' policy. Coming from Germany I had quite some trouble adjusting to this. So much trouble in fact that I just didn't come by and you two came by the internship room more than any of the other supervisors. In the end I got the message and you couldn't get rid of me anymore. I still cherish the weekly meetings we had in the morning in **Pieter's** old office where the 3 of us were writing up equations for the A matrix of our inertial OFC model. It's been quite some time since then.

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do it again!" Words that I can now understand much better than I used to. **Ivar**, we were always goofing around when we saw each other in the hallway. I couldn't understand you were wearing shorts and a t-shirt and you couldn't understand why I was wearing my winter jacket. And all this aside, there were always pull ups at the door frame! **Frank**, man I don't even know where to start. You were my office mate for so much time and I couldn't have been luckier! The advice you gave me during a frustrated period or simply that you were listening and knew how it feels like to be stuck. You were always 'there', but not often in the office. Talks about science and more often not about science were and still are a lot of fun! Thanks to you and Verena, I also met **Roemer** at SFN, Washington D.C. 2011. **Roemer,** I miss you man. The fun times we had the joking and semi-serious conversations about life and science, of course. I still want to visit you in San Diego or at least once board down a mountain together (deep snow!). I'm very glad that I have met you!

Before coming to Nijmegen I was talking to a fellow student colleague of mine from the Cognitive Science Bachelor. He told me that he was going to do his masters in Nijmegen, after which my answer was 'you're joking'. This was followed by exactly the same words, just said by the other person. You were here with me from the start man and I couldn't have asked for someone better. **Christian**, your fun persona made it so much easier for me to call Nijmegen home. You lived right next door and there wasn't a day we didn't hang out. BBQ, Flunky Ball, Männer Tag, cooking sessions, faulty Bolognese Sauce, Tiara, Ballerina shoes, dom-peridon, and the never ending discussion about reading books and my mockery of Siddhartha (maybe I should give it another try). I loved it all and I know there is so much more to come. My dear friend, I've known you now for more than 10 years and hope that there are so much more to come! Thank you so much for everything that you have done.

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During all this PhD work there was also time for a bit of vacation. First vacation ever during that time was snowboarding with **Jonathan**, **Miyuki**, **Michalis** and **Svetlana**. You guys, it was so much fun that we had to go again together, this time Greece - Roadtrip through Peloponnese. My first time in Greece ever and it was simply amazing. The scenery, the freddo cappuccino, the food ooohhh the food! I have missed it so much eating great food and be surrounded by people who enjoy it just as much! We have to try to get together again for something like this, we just have to.

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ABOUT THE AUTHOR

Adjmal Sarwary was born on 11 July 1985 in Kabul, Afghanistan. Growing up in Germany, he started studying Cognitive Science in 2005 at the University of Osnabrück. There, he finished his bachelors degree with a dissertation that resulted in a publication titled: 'Developmental Changes in Natural Viewing Behavior: Bottom-Up and Top-Down Differences between Children, Young Adults and Older Adults'. This was acomplished under the supervision of Alper Açik and Peter König. As a next step he started with the research master in cognitive neuroscience at the Radboud University Nijmegen in 2009. In his second year he began his internship working in the sensorimotor control lab with Pieter Medendorp and Luc Selen. He graduated with a masters degree in 2011. The masters dissertation was also published and titled: 'Vestibular benefits to task savings in motor adaptation'. After his undergraduate studies, he started a PhD in 2011 under the supervision of Pieter Medendorp, Luc Selen and Dick Stegeman on mechanisms of motor memories, of which this dissertation is the result. He is currently working as a postdoc researcher at the Donders Institute, Centre for Cognition.

PUBLICATIONS

- Açık A; Sarwary AME; Schultze-Kraft R; Onat S; König P (2010). *Developmental changes in natural viewing behavior: bottom-up and top-down differences between children, young adults and older adults*. Frontiers in psychology, 1, 207.
- Sarwary AME; Selen LPJ; Medendorp WP (2013). *Vestibular benefits to task savings in motor adaptation*. Journal of Neurophysiology 110, 1269–1277.
- Sarwary AME; Stegeman DF; Selen LPJ; Medendorp WP (2015). *Generalization and transfer of contextual cues in motor learning*. Journal of Neurophysiology:jn.00217.2015.
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